MECHANISMS OF HYPERTENSION

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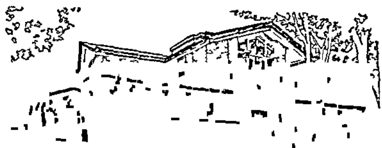
MECHANISMS OF HYPERTENSION

With a Consideration of Atherosclerosis

By

HENRY ALFRED SCHROEDER, M.D., F.A.C.P.

Associate Professor of Medicine and Director Hypertension Division Department of Internal Medicine Washington University School of Medicine Assistant Physician Barnes Hospital Saint Louis Missouri



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PREFACE

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We cannot apologize for putting forward working hy potheses which fit the evidence Far better it is to have them disproven than to attempt no elucidation of mecha nisms of disease and thus remain free from controversy— for out of controversy settled comes progress

In any disorder involving a single mechanism there are many secondary disturbances dysfunction of specific organs general metabolic changes manifest in bizzare and unpredictable signs and symptoms reactions of the whole and part of the organism to these changes attempts to reverse them by natural processes Often these disturbances mislead from rational deductions Not until the basic pathophysiologic mechanism is understood and treated do the secondary and tertiary manifestations fall into their proper places and carts begin o follow horses Because arterial hypertension can be successfully controlled some of its dependant manifestations are better understood furthermore the fact of treatment has led to a strengthen ing of hypotheses and has pointed out the way to more

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more important of them Therefore a wide latitude of choice and personal preference was left to the author, who has tried to refer to the pertinent and significant observations with which he is familiar

The physical vascular factors operating in chronic hypertension are not thoroughly discussed By and large they are understandable natural consequences and not directly pertinent to the basic problem and its treatment, although they cause most of its death and disability Statistical correlations of the disease and its effects have also been avoided Descriptive clinical data does not belong in a book on mechanisms unless they are pertinent to understanding Nor is the extensive demographic literature listed more than indirectly

Hypertension as used in this book is a state of generalized vasospasm associated with an adequate cardiovascular apparatus An arbitrary division of what is hypertension and what is not has been made a diastolic blood pressure of 90 mm Hg or more is employed as an index of vasospasm We do not subscribe to one currently popular theory that the diastolic pressure increases normally with age and that levels at age 70 which would be high at 20 are normal They may be average mean or usual, but they are by no means normal even if they can be shown to do little harm Just because a disease or a disorder is prevalent in a population does not make it normal Atherosclerotic plaques in the aorta are not normal although they are almost universal in Western Civilization As long as healthy human beings can be found on this earth who do not show a progressive degenerative disease linked to age its wide prevalence in other areas makes it be classified as a disease and treated as such

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Chapter I

THE COMPLEX OF FACTORS IN THE HUMAN DISEASE

INTRODUCTION

Arterial hypertension is only a sign of disturbed hemodynamics At the basis of this disturbance is generalized vasospasm Without vasospasm the diastolic blood pressure would not rise significantly (1)

Generalized vasospasm is a condition common to a number of hemodynamic disturbances Whenever effective blood flow through vital organs is reduced a series of reactions is set in motion aimed at restoring flow through those organs at the expense of other less essential ones Thus vasospasm follows hemorrhage precedes and accompanies shock severe coronary occlusion heart failure and other states of circulatory embarrassment It even accompanies the upright position to a small degree In these conditions blood pressure is normal or low and effective circulating blood volume and cardiac output low the vasospasm accompanying the reduction in circulation Only in late irreversible stages of shock is vasospasm replaced by vasodilatation or its capillary counterparts If the peripheral circulatory state of vasospasm remained constant and effective circulating blood volume or cardiac output were returned to normal hypertension would ensue

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This young woman s vascular response to the stress of an examination and to the pain of ice water was almost certainly mediated through the sympathetic nervous sys tem She was one of those individuals very common in the population who react to stress by vasospasm Her blushing was characteristic of a diencephalic discharge

The physician did nothing but suggest an annual phys ical examination for which she regularly returned. She had two uneventful pregnancies At the age of 32 her previously labile blood pressure was found to be 160/100 mm Hg or thereabouts not returning to a normal di astolic with rest As each year passed, a slightly upward trend was observed At 40 it varied around 180/110 mm Hg Her mother died of a stroke of apoplexy at the age of 62 which upset her emotionally She went to another physician who found her blood pressure 200/116 and told her that she had high blood pressure This was the first she knew of it and she became very agitated saw her original physician in an excited state and he measured her blood pressure at 230/140 mm Her fundi oculi showed spasm but no other changes He put her in hospital upon which her pressure fell to 160/100 mm measured

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This sequence of events leading to early death can be reconstructed in the light of what is known For many years this woman reacted to stressful situations by neurogenic vasospasm Slowly the reversibility of this alteration became less and less some gradually increasing factor being added which maintained a basal blood pressure at higher and higher levels upon which was engrafted a widely fluctuating neurogenic component This added factor was what killed her Perhaps she would not have died so early were it not for another disease atherosclerosis which began probably after her menopause and affected her cerebral arteries to such an extent that one ruptured under the high pressure

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This man suffered from the accelerated phase ' or what is more exactly and descriptively called malignant hypertension and died young He had the constitutional make up of the hypertensive person to which was added chronic low-grade smouldering pyelonephritis with an organism which does not produce pus but causes scar tissue These two factors operating together shortened his life By the time he died there was little evidence left of the primary renal disease in the kidney distorted by nephrosclerosis

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In her case a functioning adenoma in her adrenal cortex was affecting both her salt and fat metabolism the former influencing her hypertension Better diagnostic methods would have allowed surgical removal

These four cases are illustrative of distinct types of arterial hypertension encountered clinically In actual practice one sees wide variations in their courses and some times bizarre mixtures If the first patient had contracted glomerulonephritis in childhood or pyelonephritis during her pregnancy or had by chance had a kink in her uretero-pelvic junction due to an aberrant renal artery with stasis and infection she probably would have exhibited more severe hypertension at an earlier age If the second had not contracted pyelonephritis in childhood he might have lived to become hypertensive in his 50 s and died of heart failure or apoplexy in his 60 s If the renal arterial

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Sequence of Development of Arteriolar Nephrosclerosis This basic lesion which by its very nature can cause renal ischemia and hypertension, is a result of hypertension In other words the altered hemodynamics of hypertension can lead to a pathologic change which further alters renal and therefore peripheral hemodynamics. The evidence is clear on this point, in rats rabbits dogs and man (Chapter V) Therefore at some point in two of our cases renal vascular disease appeared after hypertension had become well established. Whether or not this secondary disease is responsible for the loss of reversibility of vasospasm is not known, but presumably it is not wholly accountable.

Comment All biological phenomena can eventually be understood in terms of physics and chemistry The remainder of this monograph is concerned largely with an examination of the biochemical alterations possibly operating to cause this disease which is so eventually fatal as a rule and which is so common to Western Civilization.

MECHANISMS OF SOME OF THE EFFECTS OF CHRONIC ARTERIAL HYPERTENSION

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This form of reacting to stress may be common to some human beings in many environments and of many races although adequate studies have not been made The old idea that a part of the population is sympathotonic and part parasympathotonic or vagotonic may have some basis of fact Different species of animals show different types of reaction to stress rats cats guinea pigs and rabbits not only exhibit opposite types but respond in aberrant ways to known pressor and depressor agents There are at least two kinds of dogs nervous overactive breeds which are hypertensive on the first and many subsequent examinations and more or less phlegmatic breeds or cross-breeds which exhibit normal blood pressures and bradycardia (21) There is little reason to believe that the human organism differs radically in its fundamental reactions from those of higher animals

Sympathotonic people are supposed to be subject to vasomotor phenomena tachycardia and cardiovascular diseases especially hypertension Parasympathotonic people are supposed to be subject to bradycardia a low blood pressure and gastrointestinal disorders *especially* peptic ulcer *Another* type of individual develops aller*gic reactions* In any population, all varieties and degrees of reactive *ability* can be expected depending probably on the amount of imbalance between sympathetic and parasympathetic nervous function and the *amount of* external stress to which individuals are exposed There may be several different constitutional *types* *we have* not observed true extrinsic asthma in a *hypertensive* person and such allergic states as hay fever and urticaria are *much less* common than in the general *population* duodenal ulcer is unusual in hypertension although *it exists* (4) rheumatoid arthritis and most malignant tumors *are seldom* encountered in a hypertensive population (22)

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Pickering lately summed up his concepts on the relation of heredity constitution and environment in hypertension (28) To get these conclusions in perspective it may be said that in its mode of inheritance blood pressure resembles height but that the size of the genetic factor is greater in the case of height. However the regression coefficient certainly underestimates the size of the genetic factor since we have been unable to allow for the day to-day variability of blood pressure and we have had to allow for the effects of age by a device which is probably valid when it is applied to large numbers but not so accurate for individuals By contrast, height shows quite insignificant variations from day to day and for a considerable span of adult existence is uninfluenced by age The difference between the size of the genetic factor in blood pressure and height is probably less than regression coefficients suggest. Even so it would seem justifiable to conclude that environmental factors are more important than hereditary factors in the pathogenesis of hypertension

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An environment considered unfavorable by the individual may be altered by moving to a new one temporary effects upon the course of moderate and mild stages have been observed The familiar fall in blood pressure when patients enter the hospital is an example How permanent this change can be is not known Minor adjustments in adverse environments especially those caused by other individuals with whom the patient is in close contact may for a time alter emotionally induced stresses (Figure 2)

Drugs especially sedatives have been employed for many years for the purpose of suppressing the emotional tension and lowering the threshold of reactions to stress As a general rule the more severe the hypertension the less effective are sedative drugs and other such influences upon the disease Contrariwise the milder the hypertension the more effective are measures aimed at the psyche and the emotional disturbance

The effects upon the course of hypertension of any one or combinations of the above approaches is directly proportional to the relative influence of these factors in the total picture Psychosomatic diseases may start as functional derangements mediated through autonomic nerves and end as organic conditions causing death Therefore while the beginning may lie in the psyche as exemplified by the

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Although Bays and Scrimshaw disagree (32) from all the evidence available we can be fairly certain that hyper tension not secondary to renal disease is a disorder fairly well confined to persons exposed to the influences of Western Civilization (4) For example it is unusual in parts of Africa (33) and China (8) very prevalent in Ameri can Negroes but rare in American Indians in the South west (34) In Uganda only 2 6 per cent of autopsied cases of heart failure were due to essential hypertension the same percentage to atheromatosis and none to coronary thrombosis renal hypertension however, accounted for 16 per cent (35) Surely one is led to conclude that en vironmental influences are of the greatest importance for in this country probably half the cases of heart failure are hypertensive in origin When viewed from this out look many discrepancies in the geographic incidence of hypertension fall into line

Comment There are three apparent facts upon which one can speculate

1 The predisposition to hypertension is inherited

2 There is an emotional overlay in the disease which may be either primary or secondary

3 The disease is confined more or less to civilized or partly civilized people without any particular ethnic cultural or social pattern suggesting that environmental factors such as food habits or contact with industrialized society plays an initiating role

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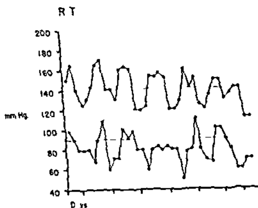


Fig 9 Daily and nightly fluctuations of supine blood pressure in an 18 year-old man in the prehypertensive phase His kidneys and heart were normal by all tests Note that the rise in pressure occurs only during the day The divisions between each 24 hour period are at midnight

The evidence against neurogenic effector mechanisms operating in sustained human neurogenic hypertension is poor and usually explicable by an analysis of the cases employed for experimentation or by an understanding of the processes concerned in neurogenic vasoconstriction [#] At present no one doubts the existence of neurogenically induced vasospasm in man We must emphasize however that in chronic human arterial hypertension the relative parts played by neurogenic and other mechanisms vary considerably from patient to patient (Chapter IV) The contrary evidence follows

1 Little or no increase in urinary catechol amines is usually found (51) Norepinephrine however is liberated at nerve endings and metabolized or conjugated *in situ* before its products reach the blood stream Therefore overproduction must be great enough to saturate oxidative and conjugative enzymes in order to allow enough to spill

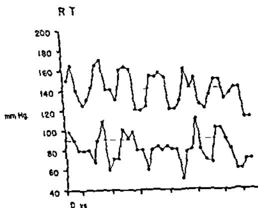


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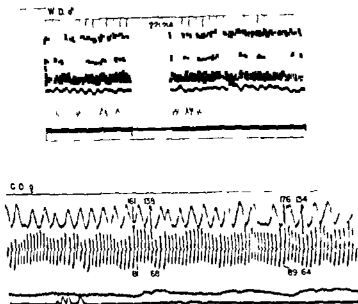


Fig. 4. Spontaneous variations in blood pressure measured photokymographically by direct arterial puncture. W. G., normal and normotensive, variation 9/6 mm. Hg. F. T., normotensive convalescent from severe acute poliomyelitis with probable slight involvement of the hypothalamus or medulla giving rise to neurogenic vasomotor instability, variation 41/20 mm. Hg. W. D., fairly severe nephrogenic hypertension, variation 13/15 mm. Hg. J. H., severe neurogenic hypertension, variation 35/25 mm. Hg. W. D. (repeat after several days rest) variation 7/3 mm. Hg. C. O., mild neurogenic hypertension, variation 42/25 mm. Hg. By indirect measurement C. O.'s systolic pressure when taken by a white coated physician varied from 180 to 240 mm. and her diastolic from 150 to 100 mm.; nurses always obtained readings 20 to 30 mm. lower. The wide fairly regular tracings are those of respiration, the smaller ones of a plethysmograph on the finger. Camera speeds 1.25, 5 and 25 mm. per second.

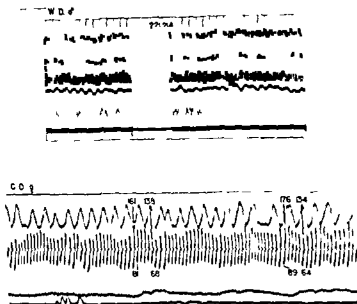


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Several influences arising in the brain can cause experimental hypertension such as noise (54) internal hydrocephalus (46) puncture of the third ventricle (55) tying off the arterial supply (19) all of which may interfere with blood flow or nervous function in a regulatory area Similarly in man increased intracranial pressure certain brain lesions of viral vascular or traumatic origin (fractures of the base of the skull encephalitis poliomyelitis) certain tumors and hypothalamic injury can lead to chronic neurogenic hypertension or its acute equivalent (56)

There are four possibilities to explain the cerebral role in human hypertension 1 The nervous temperament of the hypertensive person with the frequent finding of anxiety and frustration may initiate repetitive discharges through the sympathetic nervous system Subnormal assertiveness obsessive-compulsive traits and anxiety are said to be common to the hypertensive personality (26 27) This hypothesis has always been an attractive one but is unproven and most difficult to investigate with the tools at hand

2 The peripheral metabolic abnormalities associated with hypertension may cause stimulation of cerebral metabolism It is known that many primary amines cause central excitatory effects Amphetamine (Benzedrine) is a good example In fact Mann and Quastel (57) suggested that the central stimulant action of *dl* phenylisopropylamine (Amphetamine) is related to its inhibition of tyramine oxidation by amine oxidase in brain On this basis Fellows and Bernheim (58) examined a large number of structurally related salts in rats and found in many instances good correlations between central stimulation and cerebral amine oxidase inhibition Clinically the excitatory actions of epinephrine and a number of derivatives are well known we have observed profound and

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SPECIFIC DRUGS

Whatever the cause of the increased nervous excitability of hypertensive patients many agents have been used to counteract it and thus produce variable effects upon blood pressure depending upon a) the relative part played by the brain b) the effectiveness of the drug and c) the ability of the patient to tolerate side effects Sedatives have been used for many years in an attempt to allay tension and anxiety They will not be discussed since their employ ment is wide

Serotonin Antagonists Reserpine causes depletion of cerebral serotonin in the experimental animal (65 66) platelet serotonin is also reduced to a low level The net effect of this agent a chemical analogue of yohimbine *is* to produce on affect the equivalent of a prefrontal lobot omy (67) *Its locus* of action appears to be pre hypothalamic and subcortical the posterior hypothalamus wherein lie the sympathetic centers is partially blocked (68) The ef fect of the drug is cumulative requiring a week or two for oral doses to act maximally *although* rapidly excreted the drug itself leaves serotonin *acceptors* in the brain blocked for long *periods* Aside from its tranquilizing action [illegible]
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TABLE 1—(*continued*)

	Reserpine (123 subjects)	*Chlorproma ine (137 subjects)*
Epistaxis	2 4	0
Blurred Vision	0	1 5
Dry Mouth	0	1 5
Heart Burn	0	1 5
Edema	7 3	5 1
Pruritus	1 6	1 5
Dermatitis	0	9 5
Jaundice	0	5 1
Hepatomegaly	0	2 2

also induced among them vivid dreams and nightmares One of the most interesting of its actions is to cause, in a sizeable percentage of people nervousness insomnia agitated depressions and suicidal tendencies (70) used to treat these symptoms in psychotic individuals it can backfire and produce them Truly this most interesting drug has begun to open up a wide field in our understanding of mental illness

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Other antimetabolites to serotonin are not used in hypertension yohimbine because of its nephrotoxicity and d lysergic acid diethylamide which produces schizophrenic like states (63 66) The most interesting are the nitroindoles which are true competitive antagonists blocking

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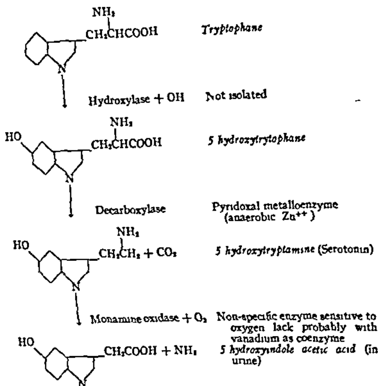


FIG 5 Metabolism of serotonin, modified from Sjoerdsma *et al* (61)

phane and its decarboxylation (Fig 5) The hydroxylase has not been discovered but the renal decarboxylase (71) contains a pyridoxal metal complex as a coenzyme (72) like many other amino acid decarboxylases. Serotonin is metabolized by monamine oxidase (Chapter IV) an enzyme requiring oxygen and sensitive to oxygen tension Therefore renal ischemia could allow the formation of serotonin by anaerobic decarboxylation but prevent deamination *in situ* due to oxygen lack Serotonin would then escape into the blood and be deaminated either in the lungs or on arterial smooth muscle While it is doubt

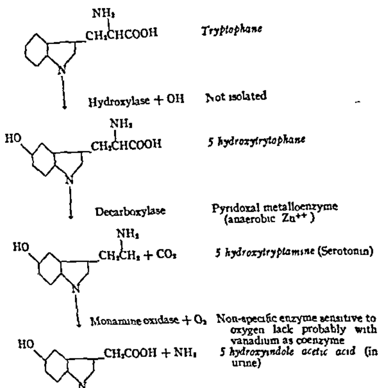


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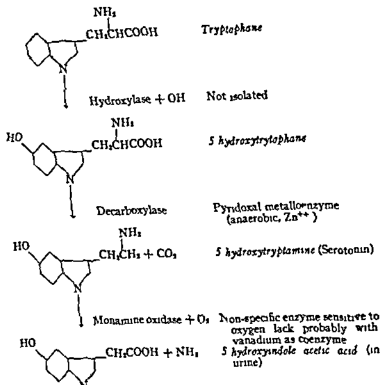


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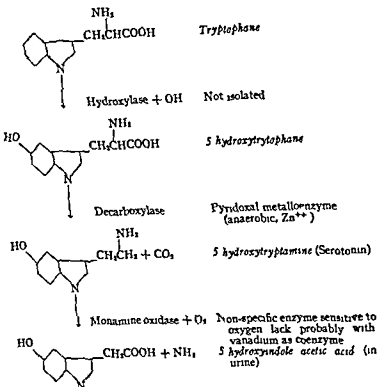


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Baroceptor Changes McCubbin Green and Page (81) have recently shown that the carotid sinus and aortic depressor mechanisms are set at a higher level of pressure in renal hypertensive dogs than in normotensive dogs They propose the ingenious theory that this higher setting maintains the hypertension even when the initiating mechanism (renal ischemia pheochromocytoma toxemia of pregnancy) is removed Thus renal hypertension slowly becomes neurogenic buffer nerve hypertension as Ogden has suspected in rats (82) If this were so in man one would expect that late chronic hypertension would respond to the use of drugs or surgery acting on nerves better than would early hypertension Clinically the opposite holds true therefore this attractive hypothesis necessarily can be discarded as applying to most human cases

SYMPATHETIC NERVOUS MECHANISMS THROUGH GANGLIA

All autonomic nerves after emergence from the spinal cord pass through ganglia In general sympathetic nerves form synapses in paravertebral ganglia while parasympa

A and B are the most purified alkaloids usually found in a mixture and most difficult to separate They cause depression of blood pressure and bradycardia nausea and vomiting may result from vagal stimulation (79) The pathway is through the glossopharyngeal nerve to the vasomotor center (78) When doses are adjusted properly, intermittent normotension can result from the careful use of protovera trine and its impure derivatives (80) Apparently tolerance is quick to appear and disappear so that sustained normotension will not result unless adjuncts operating on other mechanisms are used Whether or not this drug is a true antihypertensive agent affecting the basic process is unclear although the hemodynamic response is quite favorable (Table II)

Baroceptor Changes McCubbin Green and Page (81) have recently shown that the carotid sinus and aortic depressor mechanisms are set at a higher level of pressure in renal hypertensive dogs than in normotensive dogs They propose (the ingenious theory that this higher setting maintains the hypertension) even when the initiating mechanism (renal ischemia pheochromocytoma toxemia of pregnancy) is removed Thus (renal hypertension slowly becomes neurogenic) buffer nerve hypertension as Ogden has suspected in rats (82) If this were so in man one would expect that late chronic hypertension would respond to the use of drugs or surgery acting on nerves better than would early hypertension Clinically the opposite holds true therefore this attractive hypothesis necessarily can be discarded as applying to most human cases

SYMPATHETIC NERVOUS MECHANISMS THROUGH GANGLIA

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or choline esters can act as transmitters is not known Acetyl choline (or its derivatives) apparently is essential for synaptic transmission in all ganglia both sympathetic and parasympathetic. Nicotine in small doses is a stimulant.

The ganglion itself governs the integrity of the post ganglionic fibres much as the spinal nuclei control the integrity of their neurons. Removal of a ganglion is probably followed by degeneration of the nerve after a few days sensitivity of the nerve ending to circulating vasoconstrictor substances develops Therefore in order to perform an adequate sympathectomy preganglionic fibres must be cut

Specific Drugs Chemical ganglionic blocking agents usually contain quaternary ammonium stabilized tetra covalent nitrogen competing with acetyl choline or other more labile nitrogenous substances Numbers of such compounds exist The simplest one of the group is tetraethyl ammonium ion known for many years as a vasodilating drug of short action Longer action is achieved by lengthening the carbon chain and doubling the nitrogen group (pentamethonium pendiomide hexamethonium) or by adding cumbersome ring structures (pentolinium chloris ondamine) All act in a similar manner differing only in duration of action and degree of gastrointestinal absorption A new blocking agent mecamylamine (Inversine) differs considerably in structure being a complex spatial molecule with trivalent nitrogen as a secondary amine It has the advantage of virtually complete absorption from the gastrointestinal tract (83) Comparative doses are shown in Table III (Fig 6)

Since acetyl choline also mediates nerve transmission to striated muscle it may appear strange that curariform

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TABLE III

COMPARATIVE DOSES OF GANGLIONIC BLOCKING AGENTS (SEVERE ADULT HYPERTENSION)

Ion	*Usual Effective Oral Dose*		*Maximum Tolerated Oral Dose*		*Duration of Action of Oral Drug*	*Usual Effective Parenteral Dose‡*
	Single Dose mg	*Daily Dose mg*	*Single Dose mg*	*Daily Dose mg*	*hrs*	*Single Dose mg*
Tetraethyl Ammonium	†	†	†	†	½–1	500
Pentamethonium	500	2500	?	?	3	25
Hexamethonium	500	2500	1000	6000	4	25
Pentolinium (Ansolysen)	100	500	800	4000	4–5	25
Chlorisondamine (Ecolid)	50	250	200	1000	4–6	15
Mecamylamine (Inversine)	10	50	25	150	4–8	10

* When combined with hydralazine

† Sublingual dose effective oral not

‡ *Initial* dose much smaller Wide variation as tolerance develops

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"picture is caused by norepinephrine secreting pheochromocytomata Therefore the neurogenic component of hypertension can be considered to be mediated by this substance '

Norepinephrine is derived either from dihydroxyphenyl serine by decarboxylation or from tyramine by hydroxylation of the benzene ring and the β-carbon The first appears the most facile method for the nerve ending to make this substance rapidly It is inactivated either through conjugation through oxidation of the amine nitrogen by monamine oxidase or by rearrangement of its molecule to form an indole nucleus through oxidation by polyphenol oxidase a copper enzyme

The ideal agent for counteracting norepinephrine has not been found There are a number of sympatholytic drugs which inhibit its action on nerve endings and which are effective for short or longer periods in experimental animals We list them only as directions for research These may be grouped roughly as derivatives of benzylamine of phenethylamine of ergot of benzodioxane and of imidazole (Table IV see page 48) All contain tertiary substituted nitrogen

Derivatives of Benzylamine Dibenamine a complex structure remotely related to norepinephrine forms tight bonds at sympathetic nerve endings preventing the action of this constrictor substance probably by *competitive inhibition* The action is prolonged *for many hours* It is moderately effective by mouth much more so *intravenously* There are many side effects in man especially on the brain Dibenamine and *its relatives are the most* effective sympatholytic agents known at present but their value in hypertension remains to be proven

Derivatives of Phenethylamine We had an opportunity of testing a group of primary amines in rats for sympath

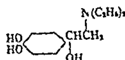
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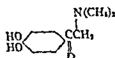
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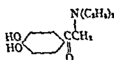
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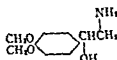
SKF 1297 A



SKF 1299 A



SKF 1300-A



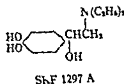
SKF 1277 A

Renal hypertensive dogs responded by a lower diastolic pressure only when SKF 1298-A was given * SKF 690 A was a powerful epinephrine like substance in man causing vasodilatation and an increased cardiac output with fall in diastolic pressure SKF 1298-A caused symptoms suggestive of cholinergic stimulation two others were without effect

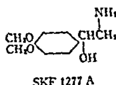
The experiments of Furchgott are of interest Using the spirally cut rabbit s aorta as a source of smooth muscle he was able to show on this simple system how certain agents such as dibenamine block all constrictor amines others block some and others block only a few (85) There fore it is likely that very specific agents can be found which will pick out one primary amine and not others for inhibition

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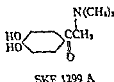
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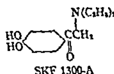
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Derivatives of Imidazole Tolazoline (Priscoline) and Phentolamine (Regitine) are two short acting moderately effective adrenergic blocking agents containing both benzene and imidazole rings Phentolamine while opposing the actions of both epinephrine and norepinephrine is useful for the most part only as a test substance for circulating catechol amines It usually causes a transient fall of blood pressure in hypertensive patients suggesting that some sympathetic tone is present in azotemia the effect may be prolonged and profound Cardiac stimulation is the rule Tolazoline is readily absorbed and excreted unchanged in the urine phentolamine is apparently metabolized up to 90 per cent of the dose The short durations of action limit their use

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The toxic or side reactions of reserpine and chlorpromazine have been given in Table I The most serious late toxic reactions of reserpine are those of agitated depressive psychosis which are often accompanied by suicidal tendencies and may lead therefore to death Of chlorpromazine there are hepatic disease and granulocytopenia some 17 deaths have resulted (92) Chronic administration of any drug given to control not cure a chronic disease may back fire Furthermore in severe hypertension the use of mild drugs is potentially dangerous giving the physician a sense of security while the disease continues relentlessly on its ravaging course

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Ganglionic blocking agents show many side effects most of them the result of parasympatholysis or sympatholysis (Table V) Only two serious ones of this nature have been encountered The first occurs when partial often asymptomatic obstruction to a hollow organ has been present Complete obstruction may result The second is concerned with the mode of excretion Absorbed blocking agents are excreted in the urine If severe renal disease is present ganglionic blockade may cause hypotension and anuria as the drug is then [illegible]

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Ganglionic blockade disease occurs in poorly treated malignant hypertension (93 94 5) it is characterized by excessive tachypnea worsened in the sitting or standing position diffuse or patchy roentgenologic changes in the lungs with few physical signs and interstitial pulmonary fibrosis at autopsy Almost all cases have exhibited azotemia (5) the microscopic findings are indistinguishable from uremic pneumonitis One patient recovered after the use of cortisone the remainder died

All of the antihypertensive agents with powerful actions can induce cardiovascular accidents due to the nature of the arterial disease (atherosclerosis) often encountered and too sudden alteration of hemodynamics Arterial thrombosis is the most serious although it is rare Such reactions are not true side effects of the drugs themselves but are inherent dangers of their overenthusiastic and careless use

Summary Because drugs acting specifically on the autonomic nervous system may affect the elevated blood pressure in human hypertension we may assume that there can be a profound neurogenic component in some cases This component probably is mediated via sympathetic nerves Although the ideal counteracting agent is not avail

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NEPHROGENIC EFFECTOR MECHANISMS

EVIDENCE FOR EXISTENCE OF OTHER EFFECTOR MECHANISMS

TO THIS point we have inferred that mechanisms other than neurogenic account for much of the generalized vasospasm seen in severe hypertensive states Although their natures are imperfectly understood there is sufficient experimental and clinical data to warrant careful examination of several hypotheses which fit or do not fit the facts

Most of the evidence for the existence of effector mechanisms other than neurogenic comes from experimental hypertension and from the wide variations in the acute or prolonged effects of drugs acting on sympathetic nerves To take up the pharmacologic evidence the following clinical observations are pertinent

1 Early and mild hypertension responds well to simple measures and milder acting sympatholytic drugs severe hypertension little or not at all

2 Extensive surgical sympathectomy either lumbodorsal or subtotal still leaves a sizeable proportion of patients as hypertensive as before relieves a fair number completely with the remainder improved to variable degrees

3 Full therapeutic doses of ganglionic blocking agents or protoveratrine cause intermittent or sustained normotension in a few cases a modified response in many and no appreciable effects (other than postural ones) in the more severe forms of hypertension

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b) Some organ is not destroying or excreting pressor substances normally present, so that they accumulate to form a new homeostatic level

" c) Some organ is sensitizing the blood vessels to normally circulating pressor substances

d) For some reason the arterial and arteriolar walls become edematous thereby increasing peripheral resistance.

Probably all of these mechanisms can operate under different clinical circumstances

The vast experimental and large clinical experience with hypertension induced by renal ischemia focuses attention upon the kidney as a mediating *mechanism for* that component of elevated arterial pressure which is not neurogenic in origin The posterior pituitary however forms a pressor substance and the adrenal cortex can sensitize blood vessels to vasoconstriction therefore endocrine mechanisms must also be considered (Chapter V) In this section we are *concerned* however with nephrogenic mechanisms

First the effects of sympathetic nervous discharges upon the renal circulation must be examined Both emotional tension and catechol amines cause renal vasoconstriction abolished in the case of the former by *sympathectomy* Curiously enough *norepinephrine* constricts in so far as is known only the renal circulation to a greater extent than other vascular beds The *hemodynamic* profile is similar to that seen in hypertension with efferent arteriolar constriction being dominant Epinephrine produces the same renal *profile* Therefore increased neurogenic sympathetic tone can cause relative renal ischemia but ischemia of no other known organ

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4 No renin or angiotonin can be found after several weeks of hypertension although the enzyme is present at first VEM in blood however increases with time to a plateau (103)

5 The oxygen consumption of the kidney may be reduced (104)

In kidneys removed from hypertensive rats and dogs the following enzymatic alterations have been demonstrated

1 Amino acid oxidation is reduced (104 105) suggesting a general inhibition of oxidative enzymes

2 Transamination is reduced in the presence of adequate pyridoxal phosphate (104) suggesting a depletion from renal tissue of apotransaminase

3 Deamination of amines is reduced (104) suggesting depletion of monamine oxidase

4 Succinic dehydrogenase and possibly cytochrome oxidase are reduced (105) All of these enzymatic alterations can be explained by loss of renal tissue consequent to prolonged ischemia

In man the following changes have been measured

1 Renal oxygen consumption is usually reduced (106 107) reflecting the ischemia

2 The urine is usually acid (108) reflecting perhaps the acidity of the cortex in ischemia

3 There is a tendency for renal loss of sodium and some chloride (109 110 4) caused in the case of sodium possibly by the acidity producing loss of base

4 The ratio of ammonia to titrable acid is lower than normal influencing possibly the sodium losing tendency of hypertensive kidneys (111)

5 Primary amines in arterial blood are usually elevated (90 91 112) a result perhaps of insufficient deamination from oxygen lack

Removal of one ischemic kidney before hypertension

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1 Amino acid oxidation is reduced (104 105) suggesting a general inhibition of oxidative enzymes

2 Transamination is reduced in the presence of adequate pyridoxal phosphate (104) suggesting a depletion from renal tissue of apotransaminase

3 Deamination of amines is reduced (104) suggesting depletion of monamine oxidase

4 Succinic dehydrogenase and possibly cytochrome oxidase are reduced (105) All of these *enzymatic* alterations can be explained by loss of renal tissue *consequent* to prolonged ischemia

In man the following changes have been measured

1 Renal oxygen consumption is usually reduced (106 107) reflecting the ischemia

2 The urine is usually acid (108) reflecting perhaps the acidity of the cortex in ischemia

3 There is a tendency for renal loss of sodium and some chloride (109 110 4) caused in the case of sodium possibly by the acidity producing loss of base

4 The ratio of ammonia to titrable acid is lower than normal influencing possibly the sodium losing tendency of hypertensive kidneys (111)

5 Primary amines in arterial blood are usually elevated (90 91 112) a result perhaps of insufficient deamination from oxygen lack

Removal of one ischemic kidney before hypertension

This is more than an academic point If hypertension were the result of chronic inhibition of a renal enzyme removal of the enzyme or removal of the kidneys would accomplish the same result. The next question is whether a precursor is altered by ischemic kidney into a pressor

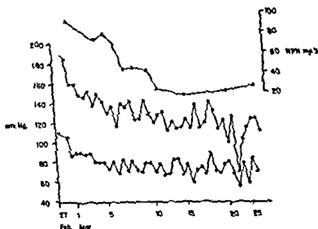


Fig 7 Azotemic hypertension with reversal when azotemia regressed Patient was a 45 year-old woman with abdominal lymphosarcoma which had involved both ureters causing bilateral hydronephrosis It was impossible to pass a urethral catheter through the left Radiotherapy was instituted, resulting in a shrinkage *of the tumor* a return of renal function toward normal *and a fall of* blood pressure occasionally to hypotensive levels

substance or whether normal kidney inactivates a pressor substance found normally in blood This question cannot be answered *except by* reference to the hypertension existing in the presence of *one ischemic* and one normal kidney The hypotheses of *best fit* include both processes retention hypertension developing with azotemia and

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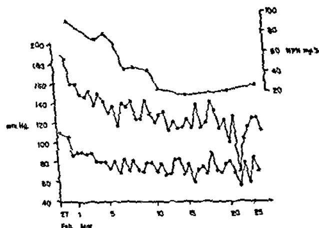


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TABLE VI

AMINO ACIDS CAPABLE OF FORMING URINARY AMMONIA*

Amino Acid	Renal Amino Acid Oxidase Present	Renal Deaminase Present	(Dog and Rat) Renal Decarboxylase Present	Renal Amine Oxidase Present
Glycine	+			
L-Alanine	+			0
L-Leucine			+	+
L Cysteine			+	?
L Methionine			?	?
L-Aspartic Acid	?		?	?
L Asparagine				
L-Glutamine		+		
L-Histidine			+	+
Oxygen required for enzyme	+	0	0	+
No ammonia formed by glutamic acid lysine or arginine				

After Meister (432)

or diamine oxidase which also acts on other diamines such as cadaverine The remainder are oxidized by monamine oxidase

Both of these enzymes are found widespread throughout many tissues. The liver is a rich source Smooth muscle and gut contain them Their ubiquitous nature is all out of proportion to their known metabolic functions

The most interesting aspect of monamine oxidase in reference to renal ischemia is its sensitivity to oxygen lack (Fig 8) Small decrements of oxygen tension inhibit enzymatic activity considerably which is not always the case for other oxidases (89) If this relationship holds in

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L-Methionine			?	?
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that passed would be distributed to all vascular organs and tissues including brain splanchnic bed and liver In so doing they would be expected to show 1) vasoactivity before being deaminated and 2) some stimulatory or depressant actions on cerebral metabolism

Bacteria in the colon have the proper decarboxylating enzymes for these amino acids and for several others The resultant amines should theoretically act on the vascular system and brain in a similar manner if absorbed That they do not usually so act can be explained by their destruction by amine oxidase in intestinal wall and in liver For it is well known that primary amines and even epinephrine can be ingested in large quantities without systemic effects adding one or more methyl groups to their side chains as in amphetamine or ephedrine however prevents oxidation by hepatic and intestinal amine oxidase allowing the drug to pass unchanged through liver and act on brain or blood vessels No orally active *amine* vasoconstricting agent lacks this side chain It is possible however that when bacterial flora are selectively inhibited by antibiotics products of intestinal putrefaction can be absorbed into the circulation from the lower colon and cause symptoms especially when the liver is damaged

The fact that extracts of arterial hypertensive blood usually contain more primary amines than those of normotensive blood (90 91) and that certain new or abnormal am[illegible]

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Since we are concerned primarily with the killing factor in hypertension and not with mild neurogenic vasospastic states it is well to examine the properties of this enzyme system further There are two which are of help in im plicating a disturbance of amine oxidation First of all amine oxidase acts on hypertensin or angiotonin (4 112) This pressor amine is a complex polypeptide (119) Second the enzyme acts on pherentasin This pressor amine is probably a polypeptide (120) If the enzyme can act on terminal amines of peptides it is possible that the formation of such peptidic amines occurs through decar boxylation and destruction by terminal amine oxidation Therefore we cannot exclude monamine oxidase in any theory of pathogenesis

This enzyme probably needs vanadium as a cofactor Vanadium occurs in three valence states and is therefore a good metal for oxidation reduction reactions being used as such by certain ascidia which concentrate it from sea water While not shown to be an essential trace element for man vanadium is found in tissues of mammals and occupies a place in the periodic table where essentiality might be inferred This subject will be discussed further in Chapter VI

Possible Role of the Lungs In order to cover other con ceivable mechanisms of vasospasm induced by humoral pressor substances we cannot *neglect the* pulmonary cir culation Any vasoactive material formed in an organ and discharged into the venous circulation must pass through the lungs before entering the area of action the peripheral arterial bed The lungs destroy at least one vasoactive

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Pherentasin has a prolonged pressor action in rats especially those with renal hypertension (91) It also constricts the smooth muscle of the isolated rabbit aorta (120) Because of its strong pressor action and the small quantities present isolation and identification has been most difficult. Much of what is known of its nature comes from inactivation studies by known agents

Pherentasin probably contains a trace metal essential for activity the nature of which is unknown It is inactivated by many antihypertensive agents not acting on sympathetic nerves (Table VII) and disappears from the blood when hypertension is controlled No one knows how it is formed.

Renin Now largely discarded the mechanism for the formation of renin by ischemic kidneys supplied an attractive hypothesis to explain chronic renal hypertension When the kidney is made ischemic renin is released into renal venous blood from parenchymal tissues possibly the juxta-glomerular apparatus (125) Thus proteolytic enzyme acts on an α_2-globulin made in liver partially hydrolyzing it to hypertensin or angiotonin * a vasoactive polypeptide As with most other more simple substances this pressor amine does not produce the peripheral circulatory profile of the hypertensive state as does norepinephrine (126 127) Unfortunately for the theory renin and its effector substances have not been found in renal venous blood of dogs or human beings with chronic hypertension They do appear however in the acute vasospastic states of acute

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TABLE VIII

COMPARISON OF PROPERTIES OF ANIMAL HYPERTENSIN AND HUMAN PHERENTASIN

Inactivation by	*Hypertensin* (*1*)	*Pherentasin* (*2*)	*Method and Remarks*
Drying	0	+	(1) can be lyophilized
Heat at pH 8 8	+	+	
Heat at pH 2 0	0	0	
Nitrous acid	+?	+	
Ninhydrin	+?	+	
Semicarbazide	?	±	(2) alters to a rapid reactant
Hydroxylamine	?	±	(2) alters to a rapid reactant
Amine Oxidase	+	+	
Tyrosinase	+	0	
Papain + cysteine	+?	+	
Chymotrypsin	+	0	
Carboxypeptidase	+	0	
Trypsin	+	0	
Pepsin	+	0	
Mg^{++}	0	0	
Mn^{++}	+	+	(1) rapid (2) slow
Cr^{++}	?	0	
Co^{++}	+	±	(1) rapid (2) partial
Fe^{++}	0	0	
V^{++++}	–	–	Both enhanced
Cu^{++}	0	0	
Zn^{++}	0	0	
Hydralazine	+	+	(1) more sensitive
NaSCN	+	+	
8-Hydroxyquinoline	+	+	(1) slow (2) more rapid
EDTA Na_3H_2	0	±	(1) 50% in 22 hours (2) 50–100% in 3–6 hours
NaN_3	+	+	
$Na_2Fe(CN)_5NO$	+	+	Rapid for both
1 benzyl 2 methyl 5 methoxy tryptamine	+	+	Serotonin antagonist

NOTE While distinct differences between these two substances are obvious the hypertensin used was probably principally hypertensin I (angiotonin) obtained from hog renin and serum Pherentasin may be hypertensin II of human origin with a slightly different structure since there is no reason to believe that the α_2 globulins of pig and man are identical

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Hydroxylamine	?	±	(2) alters to a rapid reactant
Amine Oxidase	+	+	
Tyrosinase	+	0	
Papain+cysteine	+?	+	
Chymotrypsin	+	0	
Carboxypeptidase	+	0	
Trypsin	+	0	
Pepsin	+	0	
Mg^{++}	0	0	
Mn^{++}	+	+	(1) rapid (2) slow
Cr^{++}	?	0	
Co^{++}	+	±	(1) rapid (2) partial
Fe^{++}	0	0	
V^{++++}	−	−	Both enhanced
Cu^{++}	0	0	
Zn^{++}	0	0	
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Vasoexcitor Material This unidentified substance has the property of sensitizing blood vessels to epinephrine when the latter is topically applied It comes from ischemic kidney and is active in minute amounts Larger quantities appear in chronic hypertension and congestive heart failure (100) Other substances such as renin pherentasin sustained pressor principle and some primary amines also have this property which may be nonspecific

Others A great many vasoactive substances have been found in urine and blood most of them eventually showing up as primary amines or more complex structures They may represent metabolic by products of the basic renal abnormality No good case for any has been proven as directly concerned in chronic generalized vasospasm (133-135 112 4)

Comment When many different substances are discovered or suspected to cause a single recognized abnormality time usually leads to the abandonment of all but one as causative factors Let us attempt to gather all of these different substances together and fit them into one unified scheme To do so we must speculate

1 Renin may be involved in experimental renal hypertension The evidence for this statement is indirect in that anti renin prepared by immunization reduces the hypertension of renal hypertensive dogs (136) Anti hog renin neutralizes hog and dog renin and canine hypertension anti monkey renin neutralizes monkey and human renin [illegible] [illegible] ese anti renins are there

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6 Alterations may occur by two mechanisms decarboxylation of a terminal carboxyl leaving a peptide amine or preferably peptide splitting leaving a terminal amine

7 The substrates as well as the renins from different species are obviously different in composition Human and primate renin will react with the substrates from all mammals tested while animal renin will not react with α_2-globulins from primates The exhibition of pressor activity of all hypertensins does not in any way mean that they are identical in chemical composition but only that they have in common an active group probably a terminal primary amine Pepsin acting on casein produces a pressor peptide pepsitensin identical in action to hypertensin There are thus many variables in species the source of a renin the source of serum α_2-globulins which almost certainly differ in composition from one species of animal to another and perhaps the nature of the plasma enzyme converting the inactive peptide into its vasoactive form The different amino acids found by various workers can be perhaps explained by the different sources from which the renin and its substrate were obtained (Table IX) Since human renin is unique to primates and since human globulins are unique to man *human hypertensin* can be expected to be unique in its composition of amino acids Therefore human hypertensin *may have only* a moderate resemblance to that obtained from horses dogs pigs and cows and could well be pherentasin

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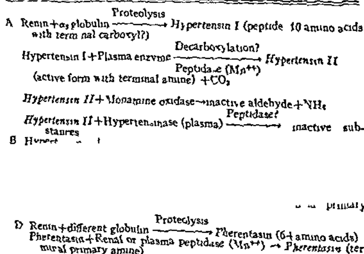
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Reaction A would thus occur in acute vasospastic states while reactions B C or D might take place in chronic states *Pherentasin* needs no serum for activity that it has at least six amino acids is based upon the findings of the active material howing six spots in chromatograms A more unitary hypothesis is that pherentasin is actually hypertensin II, a matter on which we have no evidence as yet

Comment The pieces of the picture puzzle are falling into place but there is need for much work to be done before the outlines are clear

Locus of Action of Pressor Substances While not directly established it is reasonable to assume that all vascular smooth muscle is constricted by the pressor sub-


A Renin + α_2 globulin $\xrightarrow{\text{Proteolysis}}$ *Hypertensin I* (peptide 10 amino acids with terminal carboxyl?)

Hypertensin I + Plasma enzyme $\xrightarrow[\text{Peptidase (Mn}^{++})]{\text{Decarboxylation?}}$ *Hypertensin II* (active form with terminal amine) + CO_2

Hypertensin II + Monamine oxidase → inactive aldehyde + NH_3

Hypertensin II + Hypertensinase (plasma) $\xrightarrow{\text{Peptidase?}}$ inactive substances

B Hypert ...

... primary

D Renin + different globulin $\xrightarrow{\text{Proteolysis}}$ Pherentasin (6+ amino acids)
Pherentasin + Renal or plasma peptidase (Mn^{++}) → *Pherentasin* (terminal primary amine)

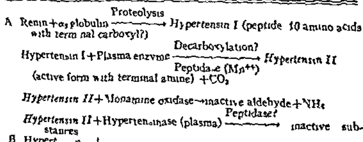
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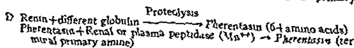
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Organic Intra renal Arterial and Arteriolar Disease The almost universal lesion found in the kidneys of patients with hypertension at necropsy is renal arterial and arteriolar sclerosis This lesion is not the cause of the hypertension however but is the result And a late result at that. About 50 per cent of patients having renal biopsies done during the operation of lumbodorsal sympathectomy had little or no arterial or arteriolar sclerosis (159) This lesion has been shown to result from hypertension produced by a variety of causes in rats (160 163) rabbits (164) and dogs (165 7) Serial renal biopsies in dogs over a seven year period have demonstrated the gradual development of the lesions only after 2 to 4 years of both neurogenic and unilateral renal hypertension the first sign being a thickening of the glomerular capsule and later an increase in material in the glomerular tuft staining with periodic acid (7)

None of these renal diseases alone can be said to cause hypertension in man until azotemia develops Hypertension is absent in 30 to 50 per cent of patients with the first two types in non azotemic stages The third type of course is the result of hypertension They do however influence it profoundly and may often alter its course to a progressive and severe one That quality which we call the ability to react to stress by vasospasm must apparently be present first and in conjunction in order for severe sustained hypertension to develop in patients with organic renal ischemia

Why then are there no more cures of hypertension

in the two groups Yuile (158) recently reviewed the literature on the relation of obstructive lesions of the main renal artery and hypertension and concluded that such a relationship does exist in certain cases This author pointed out the desirability of closer anatomical and physiologic correlation

Organic Intra renal Arterial and Arteriolar Disease The almost universal lesion found in the kidneys of patients with hypertension at necropsy is renal arterial and arteriolar sclerosis This lesion is not the cause of the hypertension however but is the result And a late result at that. About 50 per cent of patients having renal biopsies done during the operation of lumbodorsal sympathectomy had little or no arterial or arteriolar sclerosis (159) This lesion has been shown to result from hypertension produced by a variety of causes in rats (160 163) rabbits (164) and dogs (165 7) Serial renal biopsies in dogs over a seven year period have demonstrated the gradual development of the lesions only after 2 to 4 years of both neurogenic and unilateral renal hypertension the first *sign* being a thickening of the glomerular capsule and later an *increase* in material in the glomerular tuft staining with periodic acid (7)

None of these renal diseases alone can be said to cause hypertension in man until azotemia develops Hypertension is absent in 30 to 50 per cent of patients with the first two types in non azotemic stages The third type of course is the result of hypertension They do however influence it profoundly and may often alter its course to a progressive and severe one That quality which we call the ability to react to stress by vasospasm must apparently be present first and in conjunction in order for severe sustained hypertension to develop in patients with organic renal ischemia

Why then are there no more cures of hypertension

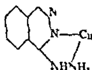
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The agents used in man are hydralazine and its deriva tives thiocyanate ion sodium nitroprusside 2 3-dimer captopropanol (BAL) sodium azide and ethylenediamine tetra acetate Of practical interest for continuous use are only the first three the effects of the other three being short lived (Table X)

HYDRALAZINE AND OTHER CHELATING AGENTS

Hydralazine and its derivatives are unique drugs No other agents known produce the same actions on vascular smooth musc - ¹
the key to
etiology of s
stood a consideration of their pharmacological chemical and enzymatic actions is necessary

Chemical Reactions Hydralazine like other hydrazides is a strong chelating agent. It will form a complex with iron copper tin vanadium, manganese nickel silver and mercury The possible structure is



making a five sided ring with nitrogen a most stable chelate *This property is shared* by isonicotinic acid hydra zide (isoniazid) and probably its isopropyl derivative

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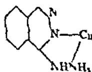
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Hydralazine is also a carbonyl reagent as are some other hydrazides phenyl hydrazine for example which forms an ozozone with glucose It will bind pyruvate acetate and acetaldehyde (168) Hydralazine has specific reactions in that no ozozone is formed with glucose or lactic acid It does not combine with any of the steroids tested (168) It is 1 hydrazinophthalazine (Apresoline)

This agent also complexes with the sulfhydryl groups on cysteine glutathione 2 3-dimercaptopropanol (BAL) and other simple mercaptans The complex can be dissociated readily by arsenic

TABLE XI A

Isoniazid * Hydralazine and Metals

	Isoniazid			
	Destruction by Me++ Auto-claving %	*Destruction by Me++ H_2O_2* %	*Binding of Hydralazine† +Me++* %	*Similarities*
Mg^{++}	0	5	0	+
Ca^{++}	0	5	0	+
Mn^{++}	100	100	87	+ Greatest at pH 6 5–7 0
Fe^{++}	50	80	22	
Fe^{+++}	40	95	100	+
Co^{++}	40	35	0	
Ni^{++}	10	15	48	
Cu^{++}	100	100	100	+ Greatest at pH 9.5–10 0
Zn^{++}	15	15	0	+

* Lewin E and Hirsch J G Studies on the stability of isoniazid. *Am Rev Tuberc & Pulm Dis* 71 732 1955

† Perry H M Jr and Schroeder H A Studies on the control of hypertension by Hyphex III Pharmacological and chemical observations on 1 hydrazinophthalazine *Am J M Sc* 228 396 1954

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TABLE XII

INHIBITION OF HISTAMINASE BY HYDRAZIDES

Substance	*Concentration Producing 50% Inhibition (molar)*	*Antihypertensive Effect*
Guanidine HCl	10^{-3}	0
Thiosemicarbazide	10^{-5}	+
Semicarbazide HCl	5×10^{-6}	?
Hydrazine SO_4	8×10^{-7}	?
Aminoguanidine HCO_3	5×10^{-8}	0
1-4 dihydrazinophthalazine	2.3×10^{-8}	+
1 hydrazino-4 methylphthalazine	2.5×10^{-8}	+
1 hydrazinophthalazine	6×10^{-8}	+

Gross F Schuler W Tripod J and Meier R Inhibition of diaminoxidase (histaminase) by phthalazine derivatives *Experentia* *8* 229 1952

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It binds strongly to arterial mash serum proteins egg albumin and some polypeptides possibly through carbonyl or sulfhydryl linkages It does not bind with casein nor with mixed amino acids

Enzymatic Reactions Hydralazine is also an anti-enzyme for several known systems It and its derivatives are strong antihistaminases theoretically preventing histamine formed from histidine from being destroyed rapidly but not necessarily causing release of histamine from histidine (Table XII) Histamine can come from the action of histidine decarboxylase believed to be a pyridoxal enzyme if so inhibition by hydralazine might be suspected Hydralazine is a potent inhibitor of DOPA decarboxylase in small concentrations also a vitamin B_6 enzyme (Table XIII) There is some evidence that histaminase itself may be a pyridoxal enzyme (169)

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TABLE XIII—(*continued*)

Substance	*DOPA Decarboxylase Millimolarity of agent*				*Monamine Oxidase (Substrate tryptamine) Millimolarity of agent*			
	10	*1*	*0 1*	*0 01*	*10*	*1*	*0 1*	*0 01*
Isoniazid	41	84	99	100	75	98	103	101
Iproniazid	108	—	—	—	14	52	91	101
Pyridoxal Isoniazid	100	114	92	91 (90)	96	101	101	101
1 5 diphenyl 3 thiocarbo-hydrazide	100	97	—	—	—	—	—	—
8 hydroxyquinoline sulfonic acid	102	—	—	—	105	—	—	—
Reserpine	102	90	92	94	—	—	115	—
β Mercaptopropionic acid	81	98	100	97	123	111	103	95
Tetrasodium pyrophosphate	86	101	97	—	95	—	—	—
Sodium cyanide	66	85	98	97	45	98	95	97
Sodium thiocyanate	89	98	100	110	100	—	—	—
Sodium azide*	91	94	—	—	115	116	98	94
Choline azide	100	—	—	—	112	104	101	101
Sodium Nitroprusside*	63	*71*	*76*	91	129	98	101	100

Italicized figures represent 20% change at 1 0 millimolar concentrations or le s considered significant

Those in parentheses show further dilutions by 10

* Antihypertensive in man Note that some of these tend to depress one enzyme and enhance the other

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TABLE XIV B

EFFECT OF ADMINISTRATION OF HYDRALAZINE ON URINARY EXCRETION OF 4-PYRIDOXIC ACID (MG) (111)

	No Subjects	No Tests	Mean Before	N Tests	Mean During	Dose of Hydralazine
Begun on Hydralazine	4	9	24 5 *(17 3–33 5)*	18	15 5 *(11 2 23 2)*	150–600
On Hydralazine for 1–3 Years	6			28	13 8 *(5 5–18 7)*	200–600
On EDTA†	3	10	22 1	15	24 0 *(22 0–26 0)*	
On EDTA and hydralazine	4			22	12 7 *(4 4–18 8)*	200–600
Normal	5	22	21 8			
Atherosclerosis	4	21	27 4			

Per 4 hours after 0 mg. orally f pyridoxal hydrochloride

† Calcium d sod um ethylenediamine tetraacetate intravenously

The ranges for each group shown in italics are the mean excretion rates of each patient

the specificity of the hydralazines for a reaction not exhibited by other hydrazides and similar agents

The known actions of hydralazine are listed in Table XV The actions of a large number of similar substances are shown in Table XIII as regards the two enzyme systems considered here

Other Metal Binding Agents Thiocyanate ion is used in industry for making soluble salts of a number of metals In man according to Sollmann (173) it ha ...

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Reactions in Man	
Lowering of plasma cholesterol	(180)
No lowering of blood pyruvate or total carbonyl	(168)
Apparent loss of Ti in urine	
Mild anemia	(168)
? Histamine release	(172)
Increases cardiac output tachycardia	(425)
Increases renal plasma flow	(426 427)

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TABLE XVI

SOLUBLE COMPLEXES OF THIOCYANATES IN WATER

Soluble	*Partly Soluble*	*Insoluble*
Mn	Pb	Cu
Fe	Hg	Ti ?
Co	Ag	Si
Zn		
Mo		
Ca		
Sr		
Ba		

Hodgman C D ed *Handbook of Chemistry and Physics* 33rd Ed Cleveland Chemical Rubber Publishing Co 1951

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British Anti Lewisite (2 3-dimercaptopropanol BAL) is used clinically to remove trace metals from the body Much is known of its actions (176 177, 178) which do not include affinities for all metals It is a disulfide chelating agent In our hands it has proven effective in causing lowering of blood pressure in American hypertensive patients for periods of a few hours On the other hand British patients have responded with a rise It is prolongedly pressor in normotensive subjects (177) but was depressor in one American hypertensive patient in the hands of others (176) BAL has little clinical use at present in hypertension In cadmium poisoning it will mobilize the metal but binding is weaker than is that of kidney for the metal is deposited and cadmium nephritis results (179) Many other heavy metals are mobilized and removed in the urine

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Mercaptan compounds which showed specific antihypertensive but not sympatholytic effects (Type A) in the rat were



$SHCH_2COOH$
Thioglycolic acid



$SHCH_2CH_2OH$
2 Mercaptoethanol

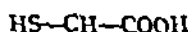


$HSCH_2CH_2NH_2$
β mercaptoethylamine



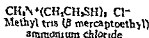
$HSCH_2CH_2COOC_2H_5$
Ethyl β mercaptopropionate

Procaine Salt of β mercaptopropionic acid

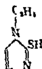




HS—CH—COOH
CH₂COOH → $HS{-}CH(CH_2COOH){-}COOH$
Thiomalic acid
(Mercaptosuccinic acid)



$CH_3N^+(CH_2CH_2SH)_3\ Cl^-$
Methyl tris (β mercaptoethyl) ammonium chloride

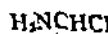


1-ethyl 2 mercaptoimidazole

Compounds showing both antihypertensive and norepinephrine blockade (Type C) were



$HSCH_2CH_2COOH$
β-mercaptopropionic acid



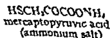






Reduced glutathione

and to a less extent



$HSCH_2COCOONH_4$
mercaptopyruvic acid
(ammonium salt)

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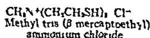


$HSCH_2CH_2NH_2$
β mercaptoethylamine

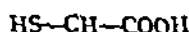


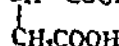
$HSCH_2CH_2COOC_2H_5$
Ethyl β mercaptopropionate

Procaine Salt of β mercaptopropionic acid

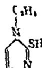


$CH_3N^+(CH_2CH_2SH)_3\ Cl^-$
Methyl tris (β mercaptoethyl) ammonium chloride





HS—CH—COOH | CH_2COOH
Thiomalic acid
(Mercaptosuccinic acid)



1-ethyl 2 mercaptoimidazole

Compounds showing both antihypertensive and norepinephrine blockade (Type C) were



$HSCH_2CH_2COOH$
β-mercaptopropionic acid



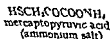






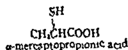
$H_2NCHCH_2CH_2CONHCH(CH_2SH)CONHCH_2COOH$ (with COOH on the first CH)
Reduced glutathione

and to a less extent

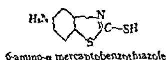


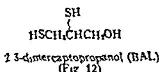
$HSCH_2COCOONH_4$
mercaptopyruvic acid
(ammonium salt)

Certain mercaptans were depressor in both types of animals (Type E) although the last two showed significant differential activities

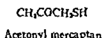

α-mercaptopropionic acid

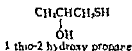

Monothioglycerol

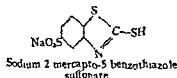

6-amino-α mercaptobenzothiazole

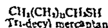

2 3-dimercaptopropanol (BAL) (Fig 12)

Only four mercaptans were sympatholytic (Type B) without depressor effects the last to a lesser degree

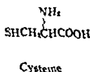

Acetonyl mercaptan

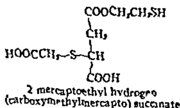

1 thio-2 hydroxy propane

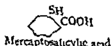

Sodium 2 mercapto-5 benzothiazole sulfonate

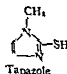

Tri-decyl mercaptan

Five were inactive or pressor the last having a short lived differential action


Cysteine

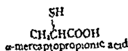

2 mercaptoethyl hydrogen (carboxymethylmercapto) succinate


Mercaptosalicylic acid


Tapazole


Pantetheine

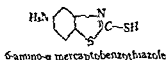
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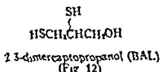
α-mercaptopropionic acid



Monothioglycerol

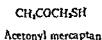


6-amino-α mercaptobenzothiazole

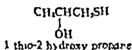


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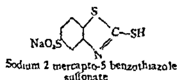
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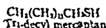
Acetonyl mercaptan



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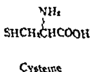


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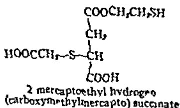


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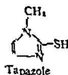
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Tapazole



Pantetheine

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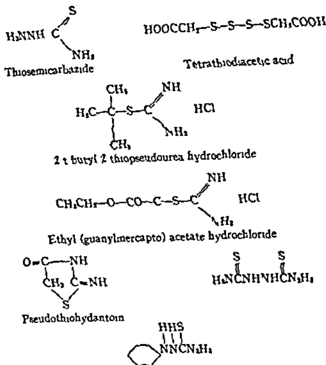


FIG 12 A. Transient effect of 2 3 dimercaptopropanol (BAL) on systolic pressure of renal hypertensive rat. Blood pressure was measured by the foot cuff method using a photoelectric cell The open circles are measurements made 2 3 and 4 hours after the injection the closed circles 24 hours later Note increasing "tolerance"

B Effect of BAL on blood pressure of a 59-year-old patient receiving hydralazine (5968) and hexamethonium chloride (C_6) in too low doses to produce normotension Doses are indicated at the top BAL, 50 mg every four hours intramuscularly was given for four doses. At the bottom urinary excretion of hexamethonium ion and hydralazine are shown The solid black areas represent free urinary hydralazine the open areas that bound to sulfhydryl All excreted hydralazine was bound after BAL was given (From Perry H M Jr Schroeder H A. and Morrow J D *Am J M Sc* 228 405 1954)

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$H_2NNH\text{—}C(=S)\text{—}NH_2$
Thiosemicarbazide

$HOOCCH_2\text{—}S\text{—}S\text{—}S\text{—}SCH_2COOH$
Tetrathiodiacetic acid

$H_3C\text{—}C(CH_3)_2\text{—}S\text{—}C(=NH)\text{—}NH_2$ HCl
2 t butyl 2 thiopseudourea hydrochloride

$CH_3CH_2\text{—}O\text{—}CO\text{—}C\text{—}S\text{—}C(=NH)\text{—}NH_2$ HCl
Ethyl (guanylmercapto) acetate hydrochloride

$O{=}C\text{—}NH$, CH_2, $C{=}NH$, S
Pseudothiohydantoin

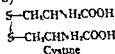
$H_2NC(=S)NHNHC(=S)NH_2$

$C_6H_{11}\text{—}N(H)N(H)C(=S)NH_2$

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Examination of the structures reveals that antihyper tensive or depressor activity was confined to those *aliphatic* compounds having a terminal sulfhydryl group or SCNH in the molecule unencumbered by a heavy salt aromatic compounds containing SCN were likewise active Such compounds usually bind metals sulfur *nitrogen binding* being strongest with Cu Ni Ag Cd and contiguous heavier elements in the periodic table These results suggest that possibly some copper enzyme was altered or inactivated causing the pharmacological activities of the compounds (182)

If this surmise be true the next step was obviously to test known chelating *agents in* the same system preferably those not metabolized If they were active obviously a metalloenzyme was altered.

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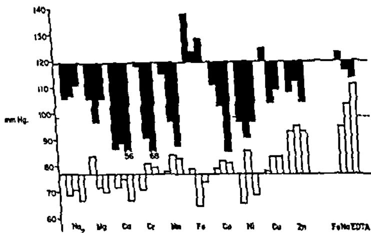


Fig 13 The effects of [illegible] eries of [illegible]
ethylene-diamin [illegible]
of hypertensive [illegible]
tized rats. The [illegible] for each *metal* complex represents the change 20 to 30 *minutes* after one intravenous injection of 5 mg the second and third changes a like interval after subsequent injections Mean chang s are shown each group representing at least 3 and usually 4 or more rats All complexes were dihydrogen metal except for ferric as shown on the right. Note the comparable differences in hypertensive (mean diastolic pressure 119 *mm*. Hg) and normotensive animals (mean diastolic pressure [illegible] mm Hg [illegible]

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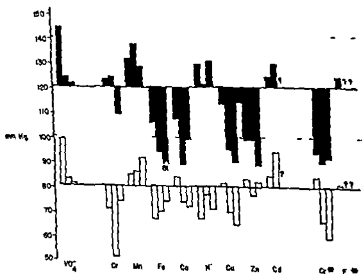


FIG 14 The effects of a series of metal ions on the diastolic pressures of groups of hypert
normotensive (mea
similarly treated. D
calcium salts were
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in Figure 1
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46 416 19 ... Clin Med

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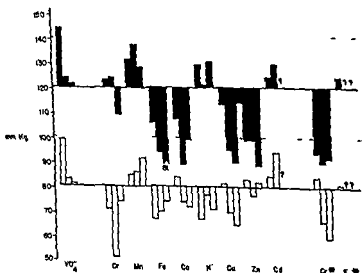


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A method for screening antihypertensive agents involves the isolated rabbit aortic strip a spirally cut piece of smooth muscle which contracts when pressor substances are applied (120) Substances acting mainly on norepinephrine and other primary amines acting on more complex pressor substances and showing general inhibition of all types can be evaluated While many agents tested cannot be applied to man their activities can be evaluated readily on isolated muscle and in the hypertensive animal A substance which is nontoxic inhibits pherentasin and lowers the blood pressure of hypertensive rats while not affecting normotension is obviously of therapeutic interest

Pherentasin Using the isolated rabbit aorta suspended in oxygenated Ringer s solution a number of these substances have been tested for their activities against pherentasin The relative degrees of inhibition are indicated in Table VII All of the metal binding agents are inhibitory On the possibility that pherentasin may be an adrenergic agent a number of sympatholytic substances

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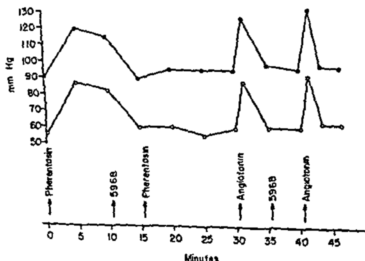


Fig 16 ^
of ph
into a
At 10
intrav
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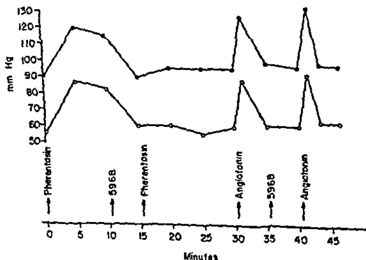


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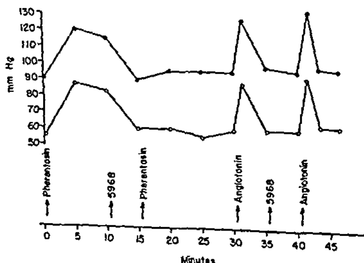


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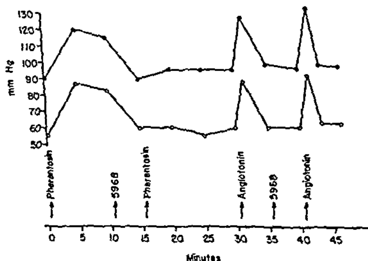


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We do not know which substance is removed from the body by hydralazine or which enzyme system or group of systems is inactivated The ability to produce this syndrome in man by a drug however suggests that lupus erythematosus itself is an enzymatic disturbance which might be affected by replacement therapy A suggestion of what has been removed in the way of metals may be obtained from trace metal analysis of human urine when hydralazine was given and from cases of known hydralazine disease and known lupus erythematosus (Table XX) The abnormal urines are somewhat low in manganese somewhat high in tin and zinc While these findings may not be pertinent to pathogenesis they deserve study Blood copper levels were not reduced in this syndrome

Of the other known functions of hydralazine carbonyl binding is the most logical to explain the toxicity It is difficult however to conceive of carbonyl binding as leading to depletion There was no diminution in total carbonyl or pyruvate in blood of patients treated with hydralazine Its other function removal of sulfhydryl is also a possible but not probable cause of hydralazine

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disease Its known antihistaminase activity and the relation of histamine to hypersensitivity is another possible explanation as is its affinity for pyridoxal

Lest the reader refrain from using this potent agent when it is needed for the prolongation of life we can say that hydralazine disease occurs in less than 10 per cent of patients and then only when relatively large doses are given that it is readily detectable easily reversible and does no permanent harm if the drug is discontinued in time There has been no mortality except in unwatched patients and the drug on the whole is hardly more toxic than many in continuous use for the control of chronic diseases The method of use is discussed in Chapter VIII

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To find the answer we must delve deeper into those mechanisms affected by ischemia in order to think of similar ones altered in the functional state Something has happened to the kidneys of patients with sustained functional hypertension which may be similarly affected in organic renal ischemia We look to altered enzymatic mechanisms to supply us with a common denominator Because ischemia is related to oxygen tension and oxygen consumption oxidative mechanisms are the first to be considered Is it possible therefore that some renal oxidative enzyme in man is reduced in function by both organic ischemia and an exogenous accumulating substance? If this were so a population might be exposed uniformly to this substance but only certain members predisposed to hypertension i e those who react to stress by vasospasm might develop permanent disease

Pickering put forth this same idea that a whole population was contaminated but only certain persons developed the disease (Chapter II) This theory is the only one consistent with the known facts and which explains the virtual absence of the disease in many areas of the world For it is likely that a proportion of all human beings react to stress by neurogenic discharges through the sympathetic nervous system

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As we have said there is obviously no generalized deficiency state which can be recognized in the American adult population Marginal intakes however are possible, especially during seasons of the year when the diet is composed largely of processed foods Converting the values in foods described in the literature to include a daily diet we have found that the intake is barely adequate (202) About 0 2 mg per 100 Gm of food is necessary to promote the growth of rats Not many foods contain this much when cooked and it was difficult to calculate a 2 0 mg intake in a sample hospital diet (202)

Why do not pronounced deficiency symptoms appear? Apparently this coenzyme has an affinity for systems where it is most needed for life and less for health Its distribution in organs shows wide variations (201) Perhaps renal deficiency can exist without deficiencies elsewhere, perhaps overloading of one vitamin B_6 enzyme system by metabolic products can produce a state of local deficiency without it being manifest in other systems The need for a coenzyme varies as the load placed upon the enzyme system as is so well known in the case of vitamin B_1 or vitamin A third possibility is that specific antagonists accumulate with age

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(Because an undesirable metal can replace an essential one in an enzyme system and inactivate it *in vitro*, it is probable that such a consequence can occur *in vivo*) In order to determine where to look we must examine the essential and the presumably abnormal trace metals in American human adult tissues and urine (Table XXI) compare them with metals found in infants to discover which accumulate with age and also compare the tissue content of people from areas not exposed to hypertension This subject will be discussed in Chapter VI but examples can be considered here

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An examination of the inhibitory effects of a number of trace metals upon DOPA decarboxylase and monamine oxidase revealed the following Some inhibition was exhibited by all in high concentrations but at low (0 1 millimolar) only cadmium and mercury significantly inhibited enzymatic activity of DOPA decarboxylase both inhibited monamine oxidase to less extent (Table XXIII) Both are nephrotoxic and will displace zinc (p 146)

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Other oxidative metalloenzymes in kidney (or elsewhere) might be affected by abnormal exogenous trace metals Two pertaining to the problem of hypertension are listed in Table XXIII (Any enzyme containing free sulfhydryl groups can be inactivated by metal binding thereon thus metalloenzymes are not essential for inactivation by metals) Direct evidence for their participation is lacking but they are shown to call attention to their role in nitrogen metabolism direct or indirect and to their metalloenzyme natures Vanadium and cadmium have striking actions

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Similarly the tubular part of the nephron may be unable to distinguish the difference between organic arterial and arteriolar narrowing from these causes or from intrarenal arterial obstruction by scars (pyelonephritis) and glomerular obstruction (nephritis and glomerulosclerosis) The locus of the mechanism reacting to renal ischemia may be postglomerular (tubular) or it may be in the juxtaglomerular apparatus which lies around the afferent arteriole In the latter case chronic glomerulonephritis might not be expected to cause hypertension until fairly widespread renal degeneration had occurred This may be the usual situation

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TABLE XXIV

VARIOUS EFFECTS OF PYRIDOXINE IN MAN WITH ESPECIAL REFERENCE TO ANTAGONISM TO METAL-BINDING AGENTS

Clinical Finding	*Induced by Metal binding Drug*	*Relieved by Vitamin B_6*	*No Reports*	*Remarks*
Convulsions	Isoniazid	Yes	1	
Convulsions	Semicarbazide	Yes	1	
Peripheral Neuritis	Isoniazid	Partly	1	Local disorder
Leukopenia and agranulocytosis	Thiouracil	Yes	5	
	Sulfonamides	Yes	2	
Peripheral Neuritis	Arsenic	Yes	1	
Cheilosis Chemosis etc	EDTA	No	1	Zinc deficiency
Same	Desoxypyridoxine	Yes	2	
Same	Spontaneous	Yes	8	
Seborrheic Dermatitis	Desoxypyridoxine	Yes	2	
Same	Spontaneous	Yes	4	Applied locally

Vitamin B_6 Selected Annotated Bibliography 1954 Merck & Co

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Experimental Steroid Hypertension For many years it has been recognized that desoxycorticosterone (DOCA) a salt retaining hormone will cause hypertension in rats when added salt is given (216 217) Likewise a syndrome similar to toxemia of pregnancy can also be produced relieved or prevented by hydralazine (218) Feeding of salt alone in excessive quantities can produce rat hypertension (219) vascular lesions result The amount of steroid and the amount of salt necessary to produce this disorder are far beyond physiologic limits DOCA is pressor in renal hypertensive dogs (220) and hypertensive patients (221) Salt restriction apparently induces adrenal cortical hyper activity (222)

Effect of Experimental Nephrogenic Hypertension on Adrenals Adrenal hypertrophy accompanies experimental nephrogenic hypertension (223) Furthermore rats with moderate hypertension voluntarily drink more saline than do normals or their paired severely hypertensive mates (224) This increased requirement for salt may be a reflection of the salt losing tendencies of ischemic kidneys already discussed in Chapter IV

Relation of Adrenal Cortex to Medulla It may not be a coincidence that the adrenal medulla concerned with the release of epinephrine and the cortex concerned with sugar salt and sex, are enclosed in the same gland. There is an intimate relationship between the two hormones acting on vascular smooth muscle There may be a further

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These interactions between nerve transmission salt vasoconstrictor substances and steroids can explain some of the clinical findings which appear on the surface to be inexplicable Normal vasomotor tone normal discharges of sympathetic fibres normal amounts of norepinephrine can produce generalized vasospasm when the vascular smooth muscle becomes hypersensitive through salt and steroids Removal of salt or steroids may restore sensitivity to normal Excessive vasomotor tone excessive discharges of sympathetic fibres excessive amounts of norepinephrine formed at nerve endings can produce a much greater degree of generalized vasospasm when the vascular smooth muscle becomes hypersensitive Removal of salt or steroids restores sensitivity to normal but does no more than partly reduce the vasospasm to a lesser level to achieve strict normality requires additional restoration of sympathetic activity to normal When the vasospasm is in part caused by circulating humoral pressor substances restoration to a normal state is impossible unless these substances are inactivated

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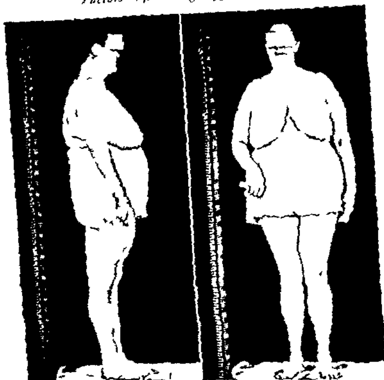


FIG 17 Central obesity, menstrual irregularities, low sweat salt (< [illegible]0 mEq/L) and hypertension. Rapid weight gain, mild hirsutism, easy bruisability and moderate diabetes were also present. This complex has been named the "endocrine hypertensive syndrome" for want of a more definitive word. The blood pressure was highly responsive to salt restriction (3, 3c)

They may be recognized by the presence of central obesity and hypertension; in women menstrual irregularities are common (Fig 17). The condition has been seen in families (3). Presumably their hypertension is influenced by an overproduction of aldosterone or other salt retaining hormones which decreases the sodium in sweat to low levels. We must hypothecate the chain of events [illegible]

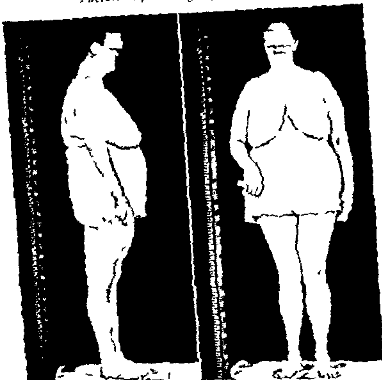


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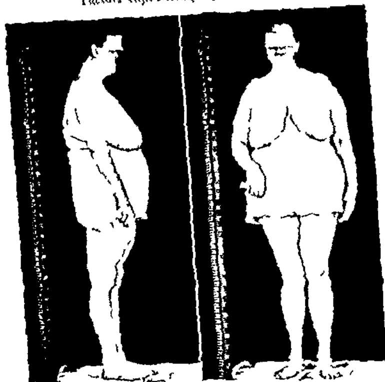


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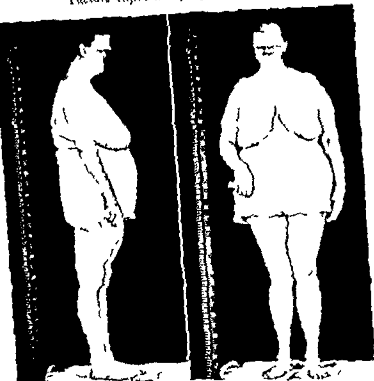


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CLINICAL IMPLICATIONS

Obviously patients with hypertension influenced by adrenal cortical overactivity should respond to restriction of salt by a lowered blood pressure They do The fact that severe s[illegible]
tension secor[illegible]
the role of th[illegible] in this state Severe salt *restrict*[illegible]

[illegible] results *do not mean that* all human hypertension is dependant upon steroids and salt on the contrary these cases are in a minority The reader must remember the simple fact that dietary salt restriction of severe degree causes overactivity of the adrenal cortex and that the usual hypertensive kidney is a salt losing kidney to an extent dependant upon the degree of renal damage or renal ischemia

Th[illegible]
hy[illegible]
frc[illegible] that case of *neurogenic* or nephrogenic hypertension Although eventually arteriolar nephrosclerosis develops a lesion dependant only on diastolic hyper

pletion or some electrolyte abnormality may be the stimu lus to the formation of aldosterone it is possible that the mild aldosteronism measured may be merely a reflection of this salt losing tendency, which probably has its seat in the kidney Slightly excessive production of aldosterone could be predicted from knowledge of chronic renal salt loss Obviously this form of adrenal cortical hyperfunction would cause if a primary initiating factor salt *retention* by the kidney a phenomenon opposite to what is actually encountered

CLINICAL IMPLICATIONS

Obviously patients with hypertension influenced by adrenal cortical overactivity should respond to restriction of salt by a lowered blood pressure They do The fact that severe s[illegible]
tension secor[illegible]
the role of th[illegible] in this state Severe salt *restrict*[illegible]

[illegible] *do not mean that* all human hypertension is dependant upon steroids and salt on the contrary these cases are in a minority The reader must remember the simple fact that dietary salt restriction of severe degree causes overactivity of the adrenal cortex and that the usual hypertensive kidney is a salt losing kidney to an extent dependant upon the degree of renal damage or renal ischemia

Th[illegible]
hy[illegible]
fr[illegible] case of *neurogenic* or nephrogenic hypertension Although eventually arteriolar nephroscle rosis develops a lesion dependant only on diastolic hyper

Chapter VI

TRACE METALS AND CARDIOVASCULAR DISEASE

INTRODUCTION

Because of the strong suggestion that trace metal im balances may be involved in some of the chronic diseases to which the people of Western Civilization are exposed a chapter on this subject is in order To be con sidered are the relations of metalloenzymes to the prob- lem the concentrations of essential trace metals in human tissues the presence and amount of abnormal metals and from whence they may come and the possibility of their interference with metalloenzymes to such an extent that they cause chronic diseases Because this subject repre sents a new frontier in Medicine vast gaps in knowledge exist but the pattern is clearing

By trace metals we will consider only those present in small or relatively minute amounts and not discuss the bulk metals sodium potassium magnesium and cal cium nor iron which has an intermediary position between ubiquitous elements and trace metals All bulk metals probably take part in enzymatic reactions or in exchange mechanisms trace metals are often confined to more specialized systems If interference with one of the bulk metals occurred in the body profound toxicity would re sult For example should all magnesium enzymes be in hibited intermediary metabolism would cease if calcium were displaced muscular relaxation would cease Partial

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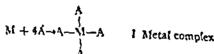
have a coordination number of 4 or 6 an index of the number of donors of the chelate with which the metal will combine Thus magnesium aluminum vanadium chromic ion manganous and manganic ferrous and ferric, cobaltous and cobaltic nickelous and nickelic tin and lead have coordination numbers of 6 while zinc cupric cadmium mercury silver gold have one of 4 and molybdenum of 8 Those of titanium and scandium have not been determined (233) Some functional groupings which bind metals are carboxyl hydroxyl carbonyl amino (primary secondary tertiary cyclic tertiary) sulfhydryl thioether sulfonate and phosphonate (232)

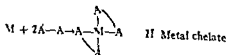
Principles of Chelation The general rules regulating the stability of metal chelates according to Bailar (234) are as follows

1 Ring structures involving metals and organic con

... rings in its presence are the most stable

3 Fused rings that is configurations in which two or more rings have a common side have a greatly increased





where M represents a metal ion A represents a complexing agent and A—A represents a chelating agent.

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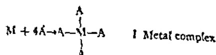
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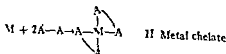
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TABLE XXV

AFFINITIES OF VARIOUS COMMON TRACE METALS FOR CHELATION BY DIFFERENT ACTIVE GROUPS

Group IIA	IIIB	IVB	VB	VIB	VIIB	VIII	IB	IIB	IIIA	IVA	VA	VIA
Be												
Mg												
Ca	Sc	Ti	V	Cr	Mn	Fe Co Ni	Cu	Zn			As	Se
Sr				Mo		Pd	Ag	Cd		Sn	Sb	Te
							Au	Hg		Pb	Bi	

Oxygen

Fluorine

Nitrogen

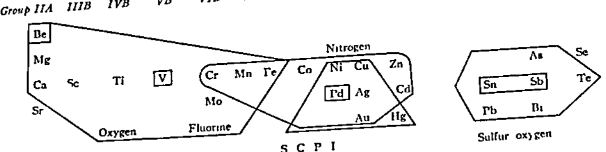
S C P I

Sulfur oxygen

After Bailar (234)

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After Bailar (234)

suggested that metal ions considered interchangeable such as magnesium manganese and cobalt are specific for en zyme activity and cannot be interchanged in the strict sense of the term

Certain metalloenzyme systems need organic coenzymes (or vitamins) for activity One possible example is pyri doxal phosphate which according to Snell requires a metal for the coenzyme to become activated (215) While the metal is not known model systems constructed without the apoenzyme suggest that either copper iron or alumi num could be the essential one (237) It is apparently so firmly bound that most metal binding agents will not re move it Other well known examples are riboflavin where flavin adenine nucleotide is intimately bound with the oxidation and reduction of iron and the copper flavinoid in acyl Coenzyme A-dehydrogenase Other members of the vitamin B group in some cases may require metals for activity magnesium with thiamine and molybdenum with flavin adenine nucleotide are examples

In general the active essential metals are divalent and in the first transitional group of the periodic table Copper is essential for phenolic and catecholic oxidation and for fat metabolism Manganese is required for peptide splitting and for carboxylation In view of the high concentrations of zinc in tissues and the very few zinc enzymes found carbonic anhydrase being the most prevalent it is possible that others exist The metallo-porphyrins are good ex amples of chelates heme the prosthetic group of hemo globin has iron chelated to four methyl pyrole rings the iron porphyrins of the cytochromes and myoglobin vitamin B^{12} has cobalt chelated in a porphyrin structure and the porphyrin of chlorophyll chelates magnesium There are several metalloproteins known ceruloplasmin and hemocuprein contain copper mercaptalbumins ap-

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TABLE XXVII—(continued)

Alkaline	Mg^{++}	Zn^{++} Co^{++} Ni^{++} Cd^{++}		
ATPase	Ca^{++} Mg^{++}			
Hexosediphosphatase	Mg^{++}			
Transphorylase	Mg^{++} $(+K^{+})$			Phosphoenol pyruvate to ADP
Flavokinase	Mg^{++}		Riboflavin	
Actomyosin	Ca^{++}			Inhibited by Mg^{++}
Arginine ATP transphorylase	Mg^{++}			
Phosphoglucomutase	Mg^{++}			
Hexokinase	Mg^{++}			
Enolase	Mg^{++} or Mn^{++}	Zn^{++}		
Dehydrogenases				
Phosphogluconic acid	Mg^{++}	Mn^{++}		
Isocitric	Mn^{++}			
Alcohol	Zn^{++}			
Oxidases				
Xanthine	Mo^{+VI}		FAD	0.03% Mo
Aldehyde	Mo^{+VI}		FAD	Only activator found†
Monamine	V^{+IV}			
Histaminase	?		Pyridoxal PO_4?	Metal not known
Decarboxylases				
5 hydroxytryptophan	Zn^{++}	Mn^{++} Mg^{++}	Pyridoxal PO_4	
DOPA	Zn^{++}		Pyridoxal PO_4	Metal inferred†
Histidine	?		Pyridoxal PO_4	
Oxalacetate	Mn^{++}	Co^{++}		
Others				
Transaminase	?		Pyridoxal PO_4	Metal not known
Uricase	Zn^{++}			

† See Table XXIII p 176 and p 154

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Arginine ATP transphorylase	Mg^{++}			
Phosphoglucomutase	Mg^{++}			
Hexokinase	Mg^{++}			
Enolase	Mg^{++} or Mn^{++}	Zn^{++}		
Dehydrogenases				
Phosphogluconic acid	Mg^{++}	Mn^{++}		
Isocitric	Mn^{++}			
Alcohol	Zn^{++}			
Oxidases				
Xanthine	Mo^{+VI}		FAD	0.03% Mo
Aldehyde	Mo^{+VI}		FAD	Only activator found†
Monamine	V^{+IV}		Pyridoxal PO_4?	Metal not known
Histaminase	?		Pyridoxal PO_4	Metal inferred†
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5 hydroxytryptophan	Zn^{++}	Mn^{++} Mg^{++}	Pyridoxal PO_4	
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have an affinity for bone both strontium and beryllium can cause rickets and beryllium displaces magnesium on phosphatases inactivating them Therefore all but mag nesium are concentrated by one tissue Similarly two anionic and all cationic elements in group VII have been shown to be concentrated by the thyroid iodine astatine manganese technetium and rhenium those of the halide sub-group quite specifically (239 242) Likewise in group V A bismuth antimony and arsenic are believed to dis place phosphorus in phosphates Gold silver and copper of group I B have strong affinities for each other as does cadmium for zinc in group II B complete separation of the two from ores is difficult and often too expensive for commercial purposes Cadmium displaces zinc on human mercaptalbumin while lead does not presumably be cause the former two ions bind the same molecular group (the 16 imidazole groups) while the latter binds at a different site Cadmium therefore has a higher affinity than zinc for this protein Similarly cupric ion is displaced from the sulfhydryl groups of bovine serum albumin by metals in the following order of affinity $Hg^{++} > Pb^{++} > Cd^{++} > Zn^{++}$ (243) Among the anions fluorine chlorine bromine and iodine are biologically interrelated while selenium and tellurium of group VII A will displace sul fur in hair and nails possibly in sulfhydryl groups In group I A radio-rubidium is used to measure potassium space (244)

Metalloenzyme Inhibitions In spite of these obvious relationships in biological material metalloenzyme com petition by an extraneous metal has not been systematically studied In Table XXVIII are shown examples of cases where an extraneous metal apparently displaces an active metallic prosthetic group The list may be far from com plete At least two types of enzyme inhibition can occur

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One is when a heavy metal combines with sulfhydryl groups to inactivate the enzyme Mercury copper and silver will inactivate many enzymes which do not contain a metal (245) Presumably, the toxic effects of many heavy metals are due to this type of reaction The second is when the essential metal is displaced by another often of the same periodic group Lerner has offered good examples of both types of reactions in respect to tyrosinase essential for formation of melanin (246) Metals which compete with copper Increased melanin pigmentation is frequently observed when heavy metals such as arsenic bismuth iron gold silver and mercury are deposited in the skin Patients with hemochromatosis have relatively large amounts of iron and copper deposited in the skin The most plausible explanation for these findings is that metals bind epidermal sulfhydryl groups and thereby re lease inhibition of tyrosinase The increased tyrosinase activity results in increased melanin formation However if sufficient quantities of the metals mercury silver or gold are present they can replace the copper of tyrosinase to produce an inactive enzyme with resultant depigmenta tion It is possible that the slight decrease in skin color produced by ammoniated mercury freckle creams is achieved in this manner Six copper binding agents have caused depigmentation *in vivo* (247) most of them anti thyroid drugs

Essential metals such as copper manganese cobalt and zinc can interact to inhibit the metalloenzymes of each Excess enzymatic activity by a presumably abnormal metal can also occur For example chromium causes increased synthesis of cholesterol and fatty acids by rat liver (248) cadmium and cobalt enhance bacterial oxalacetic carboxy lase a manganous enzyme vanadyl ion enhances mona mine oxidase (Table XXIII) Thus both stimulation and depression by abnormal metal are possible

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Each chelating compound differs widely in its affinity for different metals In Table XXIX are shown the stability constants of a number of common oxygen and nitrogen chelators with divalent metals of the first transitional group and with cadmium Ten of these compounds are present in biological fluids In general an increase in tightness of structure is proportional to atomic number reaching a peak at copper (or nickel) and decreasing thereafter This fundamental property of most chelating agents must be in mind whenever they are used in effect this property means that a free ion having a higher stability constant with the chelator will displace a chelated metal with a lower constant When the active groups are sulfur and other chelators the pattern of metallic affinity is different (Table XXV)

Metal Binding Simple metal binding is dependent either upon the tightness of the bond the lack of dissociation of the dissolved salt or upon the insolubility of the complex Thus complexes may be formed between metal and ammonia metal and sulfhydryl metal and cyanide or metal and hydroxide The stability constants for transitional metal complexes in solution are usually lower than for chelates although mercury has a fairly high affinity for CN NH_3 OH and pyridine The common law relating the stabilities of chelates of the first transitional group and atomic numbers appears to operate in the case of simple complexes of OH CN NH_3 and pyridine

DRUGS AS CHELATING AGENTS

Most potent drugs may act through their abilities to chelate trace metals on metalloenzymes Schubert states

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Many chelating agents are fungicidal antiseptic or bactericidal (233) Thirteen of nineteen common organic chelators of one or more transitional metals are listed by Martell and Calvin as effective against growth of B subtilis with seven against growth of B Coli Likewise, 8-hydroxy quinoline of seven quinolines and 26 substituted quinolines of 35 are effective against the growth of clostridium welchii *most of which inhibit* streptococcus hemolyticus staphylococcus aureus and B Coli less so proteus and pseudomonas pyocyaneus *Zinc* and manganese appear to be bound although the other essential metals iron and cobalt may be involved Apparently copper is not for copper reagents in general are inert Few are effective against pyocyaneus *an organism* resistant to most antibiotics The fungicidal properties of the oxines so widely used in industry is believed to be the result of their chelation with zinc [illegible]

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chelation

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An example of the effects of EDTA given intravenously to two patients is shown in Table XXX Zinc was removed in sizeable quantities other metals less so or not at all The high excretion of zinc in the patient with the nephrotic syndrome found before the drug was given is probably explained by the excessive proteinuria which carries combined zinc There was no mobilization of lead while

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BAL (2 3-dimercaptopropanol) a straight chain dithiol binds the following heavy metals in a chelate zinc chromium cadmium nickel, lead, antimony, arsenic, bismuth copper, mercury, gold (251) Substitution complexes on the sulfhydryls are formed In the case of cadmium at least, these are dissociated in the kidney and may result in cadmium nephritis a reflection of the greater binding capacity of renal tissue for cadmium than BAL Citrate a chelating agent used for lead poisoning is metabolized by the body and is therefore relatively ineffective A list of some representative binding and chelating agents is shown in Table XXXI Their use in medicine is only beginning For example all antithyroid drugs have this common property suggesting their probable action

These considerations open up a wide field of thought on the mechanisms of disease and of drug actions Similar conclusions can be drawn when late toxic reactions of drugs are compared with structure The common denominator of the offending drugs appeared to be in chelation

Drug Reactions Late systemic reactions to drugs affect several organs and systems of which blood dyscrasias hepatitis and polyarteritis are the most serious (252) Most of the drugs causing fatal agranulocytosis as listed by

[illegible] procaine amide and Tapazole containing pyridines amines amides nitroso or sulfhydryl groups (253) Their solubilities and specificities for heavy metals however are not known to our knowledge Nonfatal leucopenia has occurred with arsenical compounds gold salts thiouracils hydantoins salicylates sulfonamides streptomycin and thiosemicarbazone which can displace or bind

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[illegible] procaine amide and Tapazole containing pyridines amines amides nitroso or sulfhydryl groups (253) Their solubilities and specificities for heavy metals however are not known to our knowledge Nonfatal leucopenia has occurred with arsenical compounds gold salts thiouracils hydantoins salicylates sulfonamides streptomycin and thiosemicarbazone which can displace or bind

TABLE XXXI—*(continued)*

Nitrite	
Thiocyanate	
Pyrocatechol	
Quinaldine	
Hydantoin	
Hydrazine	
Chelating Chemicals *	
Phytic Acid	
2 ketogluconic acid	
Glycerophosphates	
Potassium gluconate	
Gallates	
Rubeanic acid and derivatives	
Guanidine carbonate	
Potassium ethyl xanthate	
Dimethyl glyoxine	
Uracils	
Oximes	
Diphenyl carbazide	
Diphenyl thiocarbazone	
Potassium thiocarbonate	
Cupferron	
Adipoin	
Some Reagents for Analysis of Metals	256
Zn Ferric cyanide	
8-hydroxyquinoline	
Quinaldinate	
Sn Dinitro-diphenylamine sulfoxide	
Toluene dithiol	
Ag P-dimethylamino-benzalrhodamine	
Ni γ benzil-dioxime	
Dithiooxalate	
Dithiol	
Mo Thiocyanate	
Cu Quinosol	
Pyridine thiocyanate	
Cd β-napthoquinoline	
Thiourea	
Benzoin-oxime	

From chemical catalogues

TABLE XXXI—*(continued)*

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Benzoin-oxime	

From chemical catalogues

causing shock 13 new ones appear which do not have this property and 13 of the above are represented Bronchial asthma caused by 36 agents of which 19 are of plant or animal origin and unidentified structurally is caused by 14 containing possible metal complexing groups or metals A similar situation appears among the agents causing severe late toxic skin reactions such as eczema urticaria exanthemata exfoliative dermatitis bullous eruptions and the like Metals and binding agents appear frequently when the chemical structure is known

Curiously enough serious local and systemic reactions are rare or absent among the drugs not containing metal reactive groups or producing them only on extensive hydrolysis Sulfobromphthalein decholin, paredrine ether boric acid Banthine menthol quotane diocaine chloral hydrate morphine opium codeine digitalis are examples On the other hand barbituric acid the basic constituent of many sedatives and a pyridine compound forms salts with metals Metal binding by sulfanilic acid is well known (233) The instability of hydantoin hydrolyzing to metal binding hydantoic acid the metal binding properties of pyridines nitroso groups (dinitrophenol is a good example) cyanides amine and sulfhydryl groups semi carbazides di carboxylic acids thiols and sulfur-containing structures appear to be related to many forms of drug sensitivity Therefore it is possible that trace metals may be involved in many reactions of sensitization and perhaps even in some forms of allergy BAL (2 3-dimercaptopropanol) for example is a potent contactant Although drug reactions vary widely in frequency such agents as dinitrophenol being very active and amines relatively inactive ...

... sulfonate etc.) the more likely

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TABLE XXXII

TRACE METALS FOUND IN MAN AND THEIR PROBABLE ROLES

Essential	*Possibly Essential*	*No Known Metabolic Function*	*Metabolic or Antimetabolic*	*Not Found But Antimetabolic*
Cobalt	Aluminum	Barium	Bismuth	Antimony
Copper	Strontium	Boron	*Cadmium*	Arsenic
Iron	Vanadium	Cesium	*Chromium*	Beryllium
Manganese		Gallium	Gold	Thallium
Molybdenum		Lanthanum	*Lead*	
			Nickel	
Zinc			Silver	
		Tin	*Titanium*	

Those in italics may be implicated in chronic diseases especially cardiovascular because of their prevalence concentrations or known functions on enzyme systems.

and satisfying certain criteria for reactivity in enzyme mechanisms can be expected to have become essential for metabolism We cannot say that living cells have learned to use new and less reactive elements in enzyme systems by a process of adaptation the basic structures of atoms have not changed and life began by using the most suitable ones

Because all food comes eventually from plants an examination of the metallic content of plants is necessary local pastural variations can be neglected No metal can be expected to be essential for animals which does not occur in plants or in water In Table XXXIII are the metals of interest in plants Little aluminum nickel and no cadmium tin silver gold titanium lead or mercury is to be expected in animal tissues while vanadium and the five known essential metals will be found Obviously if domestic animals or man show appreciable quantities of those which do not appear in plants they must have come from unnatural sources

To be classed as abnormal for our thesis a metal

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To be classed as abnormal for our thesis a metal

a) should be found in human tissues from some areas of the world and not from others b) should not be found in plants or wild animals c) should affect some metallo-enzymes d) preferably should not be in the tissues of young infants e) should be introduced by the habits of Western Civilization into foods or beverages as a result of proces sing transportation or manufacture and f) should be poorly excreted cumulative and preferably showing organ specificity

Concentrations of the Essential Trace Metals in Man Although many analyses have been done by various meth ods for single or several elements in blood tissues and urine (254 257) the first extensive systematic investiga tion on the content of both essential and abnormal trace metals in human tissues was made by Tipton and her co workers Using spark spectrographic methods with indium as an internal standard and densitometric *photo*-electric recording of plates Tipton analyzed 258 tissues from 24 persons dying suddenly in various areas of the United States for 18 metals (almost 4500 analyses) *(231)* A preliminary analysis of 42 autopsies from various places *in this* country showed similar but less quantitative re *sults* (258) while in a later series the findings *were essen* tially the same (259)

In Table XXXIV are the mean concentrations in vari ous tissues of the *essential* elements manganese cobalt *copper* zinc and molybdenum calculated roughly for total bodily amounts Zinc is the most prevalent of the normal *group in several* times the concentration of any of the others Essential cobal*t was found* in only five bodies sparsely scattered in small *concentrations* probably because of methodological limits and its presence in very minute quantities These *results* appear comparable to those of Griffith *et al* for copper zinc and manganese on

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the basis of dry tissue in a much larger series (260)

Some organs concentrate certain metals others do not Zinc was found in every organ in concentrations of 4 4 to 300 mg /Kg being far highest in prostate then muscle liver kidney and heart and lowest in adrenal bladder brain testis lung and intestine Copper was concentrated in brain liver and spleen being lowest in muscle adrenal aorta intestine and testis Manganese in much smaller amounts was concentrated especially in liver with pan creas lung spleen and thyroid following quite far behind lowest organs were heart muscle testis and aorta Three of these four metals were found in all 258 specimens examined Molybdenum was absent in only half of the samples of muscle and testis a third of those of pancreas thyroid and lung most prostates and all but one brain but was found in concentrations of more than 0 13 mg /Kg in all heart kidney and liver samples being by far the highest in liver In the concentrations detectable, molybdenum apparently is not essential for metabolism in all organs but three of the others may be

Sources and Turnover of Essential Metals All of the essential trace metals are found to a greater or less extent in plant and animal tissues (Table XXXIV) derived from the soil Cobalt is probably the least concentrated Soils vary widely in their contents of trace elements and disorders due to deficiencies or excesses have been recog nized in both plants and animals Semi-quantitative trace mineral analysis is a recognized practice in the evaluation of soils for farming The following was summarized from Monier Williams (256) and Marston (261)

Manganese The largest sources are in the following foods with above 30 mg /Kg oatmeal whole meal flour bran soy bean meal cocoa cloves chestnuts pepper maple sugar tea contains 150 to 900 mg /Kg With lesser con

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may also be important in hemoglobin formation A copper enzyme ceruloplasmin is found in concentrations of about 34 mg per 100 ml of serum Several phenolic oxidases depend upon copper pigmentation may be related to the content in skin and hair follicles Copper is quite well re tained by the body with some dependency upon intake, being slowly eliminated by way of the feces Gallstones contain large amounts No chronic copper poisoning has been described in human beings Human milk is extremely low in content 0 04 mg /Kg As a rule American foods contain adequate amounts sometimes an excess since many insecticides and fungicides contain copper The largest amounts 10 mg /Kg or more are found in tea coffee cocoa chocolates, nuts liver shell fish especially oysters tomatoes and yeast The least is found in milk butter cheese refined sugar honey margarine lard and suet

Zinc This most prevalent of the trace metals in the hu man body is present in large quantities in most organs as seen in Table XXXIV It is found in foods and is a requirement of plants bacteria and fungi Most modern fungicides are zinc chelating agents Deficiency in soils causes diseases of both plants and animals although its prevalence makes animal diseases more uncommon Foods with over 50 mg /Kg are wheat germ bran oysters beef livers gelatin and dried eggs those which contain the least amount are fruits chestnuts green vegetables and fish Chronic poisoning in man is *not known* There have been several outbreaks of supposedly acute poisoning from foods stored in zinc lined receptacles but the contamina tion of zinc by cadmium makes it questionable that zinc itself was the cause symptoms of zinc and cadmium poison ing are identical i e violent gastroenteritis and zinc poisoning is most difficult to produce in animals

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high content of iron in their livers Apparently the bacteria in the rumen synthesize vitamin B_{12} when cobalt is present high requirements are indicated by the large doses of the vitamin necessary to cure this disease Horses and pigs raised in the same deficient areas are not affected as their requirements are lower Bacterial synthesis in the colon, as occurs in man apparently does not lead to absorption of this vitamin, therefore it must be ingested as such *Copper* deficiency has been implicated in certain anemias in infancy but no known diseases in adults have been described Anemia has been produced in laboratory animals along with a slow rate of growth impaired absorption of ingested iron impaired mobilization of iron from tissues and impaired utilization of iron for hemoglobin synthesis have been found, as well as low *cytochrome oxidase* activity of the bone marrow Cattle grazing on copper-deficient pastures show depigmented, abnormal hair develop cachexia anorexia and anemia their bones become fragile reproduction and milk production is decreased and they frequently die of cardiac failure young animals may become ataxic Sheep show defective keratinization and hypochromic anemia lambs born of copper deficient ewes develop swayback and ataxic and paralytic diseases characterized by diffuse demyelinization of the central nervous system Depigmentation has been produced in many species Excesses or deficiencies of other trace elements may influence the disorders in cattle and sheep especially of cobalt and molybdenum *Molybdenum* deficiency prevents fixation of nitrogen by soil bacteria [illegible]

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TABLE XXXV

CONCENTRATIONS AND CONTENTS OF ABNORMAL TRACE METALS WITH ORGAN SPECIFICITIES

(WET WEIGHT) (231)

Organ	Cd mg/Kg	Cd Total mg	Al mg/Kg	Al Total mg	T mg/Kg	T Total mg	Pb mg/Kg	Pb Total mg	B mg/Kg	B Total mg
Adrenal	1.24	0.02	4.41	0.09	0.52	0.01	1.04	0.02	(0.37)	0.108
Aorta	1.09		9.09		0.75		1.05		(0.19)	
Bladder	(0.93)	0.10	2.53	0.5	0.23	0.04	0.39	0.09	(0.8)	0.05
Brain	0		3.55	1.1	(0.0)	0.14	0.31	0.62	0	
Heart	(0.74)	0.52	2.51	0.5	0.13	0.03	0.98	0.9	—	
Stomach & intestine	1.20	2.40	3.25	6.50	0.44	0.88	0.58	1.16	(0.26)	
Kidney	33.1	9.93	1.80	0.54	0.44	0.04	1.27	0.38	—	
Liver	3.60	5.40	2.55	3.84	0.6	0.49	2.04	3.06	—	
Lung	(1.73)	1.1	30.8	21.6	7.65	3.56	1.23	0.85	—	
Muscle	(1.78)	49.8	3.01	54.2	0.48	13.4	0.71	19.9	—	
Pancreas	2.10	0.21	2.67	0.21	0.16	0.02	1.32	0.13	(0.41)	0.03
Prostate	(1.55)	0.08	5.55	0.28	1.51	0.08	0.29	0.05	—	
Spleen	(1.96)	0.39	3.34	0.67	0.31	0.06	1.33	0.27	(1.0)	0.4
Testis	(1.31)	0.03	5.8	0.09	0.21	0.004	0.67	0.01	—	
Thyroid	2.08	0.06	5.13	0.15	0.37	0.09	0.50	0.02	0	
Skin, Skeleton, Adipose Tissue, Other Tissue	3.88	46.6	3.35	66.2	0.87	10.68	0.90	10.8	(0.18)	2.16
Sub Total known (mg)		0.4		96.56		20.48		20.80		0.338
Total with estimated skin and other soft tissue at mean value X(70 kg (mg))		116.84		160.76		31.14		37.60		2.338
Specimens lacking metal	76		3		11		0		159	

Figures in parentheses indicate the metal was missing in two or more samples.
* Half or more of specimens ...ly

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Organ	Cd mg/Kg	Cd Total mg	Al mg/Kg	Al Total mg	T mg/Kg	T Total mg	Pb mg/Kg	Pb Total mg	D mg/Kg	D Total mg
Adrenal	1 24	0 02	4 41	0 09	0 52	0 01	1 04	0 02	(0 37)	0 108
Aorta	1 09		9 09		0 75		1 05		(0 19)	
Bladder	(0 93)	0 19	2 53	0 5	0 21	0 04	0 39	0 09	(0 4)	0 05
Brain	0		3 55	1 1	(0 0)	0 14	0 31	0 62	0	
Heart	(0 34)	0 52	2 51	0 5	0 15	0 03	0 98	0 9	—	
Stomach & intestine	1 20	2 40	3 23	6 50	0 44	0 88	0 58	1 16	(0 26)	
Kidney	33 1	9 93	1 80	0 34	0 44	0 04	1 27	0 38	—	
Liver	3 60	5 40	2 55	3 85	0 6	0 49	2 04	3 06	—	
Lung	(1 73)	1 1	30 8	21 6	7 65	3 36	1 33	0 85	—	
Muscle	(1 78)	49 8	3 01	54 2	0 48	15 4	0 71	19 9	—	
Pancreas	2 10	0 21	2 67	0 21	0 18	0 02	1 32	0 13	(0 41)	0 03
Prostate	(1 55)	0 03	5 55	0 28	1 51	0 08	0 29	0 03	—	
Spleen	(1 96)	0 39	3 34	0 07	0 31	0 06	1 33	0 27	(1 0)	0 4
Testis	(1 31)	0 03	5 8	0 09	0 21	0 004	0 67	0 01	—	
Thyroid	2 08	0 06	5 12	0 15	0 37	0 01	0 50	0 02	0	
Skin, Skeleton, Adipose Tissue, Other Tissue	3 88	46 6	3 35	66 2	0 87	10 68	0 90	10 8	(0 18)	2 16
Sub Total known (mg)		0 4		96 36		20 46		20 80		0 338
Total with estimated skin and other soft tissues at mean value X (70 kg (mg))		116 84		160 76		31 14		37 60		2 398
Specimens with metal	76		3		11		0		159	

Figures in parentheses indicate element missing in two or more samples.
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ubiquitous elements tin nickel, chromium and silver (Table XXXVI)

The obvious conclusions are that relatively large amounts of cadmium are in American kidneys and aluminum and titanium in lungs while other metals are more or less evenly distributed Furthermore there is weight for weight more of several abnormal metals in most organs than normal ones of high biological activity such as manganese copper and molybdenum On the basis of mass alone these three tables show the following when the metals are arranged according to the periodic table Silver is present in amounts equal to 2 2 per cent of copper cadmium equal to 12 per cent of zinc (50 per cent in the kidney) chromium equal to 61 per cent of molybdenum (and is more prevalent) nickel equal to 140 per cent of cobalt while there is more titanium tin and lead than manganese molybdenum and cobalt and there is more aluminum than copper Thus the order in decreasing amounts is *Zn* Al *Cu* Cd Pb Ti Sn *Mo*, Ni *Co*, Cr *Mn* Ag B according to the present estimate (essential ones in italics) Traces of gallium were found in most lungs of bismuth in 21 samples of gold in 72 samples and of thallium in 6 samples

In Tipton s second series of 24 autopsies from another (western) part of the United States (259) the findings were quite similar for the essential metals although there were somewhat less copper and zinc in most organs and molybdenum was largely confined to liver and kidney Of those now considered abnormal cadmium appeared in liver and kidney in the same concentrations as in her first series but a large majority of other organs were lacking in this element There was much less aluminum in all organs but lung (23 mg /Kg) and titanium was found in only a few bodies except for lung where its concentration

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(266) There were 4 kidneys and livers 3 lungs 2 spleens and 1 aorta heart intestine and muscle In contradistinction to adult tissues kidneys and livers and lungs contained no titanium cadmium or tin Aluminum was not concentrated in lung although it occurred in amounts of 0 3 1 0 mg /kg in most tissues less than that of adults Titanium was found in only one body in intestine kidney and muscle Nickel occurred in one other kidney and liver tin was in both spleens and the sample of muscle and aorta On the other hand boron was in all tissues but one kidney and liver chromium and silver were ubiquitous in adult concentrations as was lead but in smaller amounts than in adults Organ specificity as determined by concentration was not found consistently *

In the bodies of 3 older infants and children (7 weeks 10 months and 2 years) there was no titanium Nickel in traces was in 1 kidney tin was found in all tissues as was lead while silver occurred in 7 of 12 specimens Cadmium was present in the 10 month-old kidney (0 65 mg /kg) and in the 2 year-old (2 75 mg /kg) but not in the 7 week old *one* The essential metals were found in distributions and concentrations similar to those of adults Manganese was if anything more concentrated zinc less so while copper was comparable showing an affinity for liver Molybdenum was in all livers while cobalt was present in only two

Within the limits of these observations, and in view of what is known the following further conclusions can be drawn 1 Titanium nickel and cadmium are not essential to infant life but accumulate with age 2 Aluminum chromium silver and lead either qualify as essential trace metals or pass through the placental membrane Obviously titanium nickel cadmium and tin do not so pass

* Analyses of 20 stillborn infants gave essentially similar results

(266) There were 4 kidneys and livers 3 lungs 2 spleens and 1 aorta heart intestine and muscle In contradistinction to adult tissues kidneys and livers and lungs contained no titanium cadmium or tin Aluminum was not concentrated in lung although it occurred in amounts of 0 3 1 0 mg /kg in most tissues less than that of adults Titanium was found in only one body in intestine kidney and muscle Nickel occurred in one other kidney and liver tin was in both spleens and the sample of muscle and aorta On the other hand boron was in all tissues but one kidney and liver chromium and silver were ubiquitous in adult concentrations as was lead but in smaller amounts than in adults Organ specificity as determined by concentration was not found consistently *

In the bodies of 3 older infants and children (7 weeks 10 months and 2 years) there was no titanium Nickel in traces was in 1 kidney tin was found in all tissues as was lead while silver occurred in 7 of 12 specimens Cadmium was present in the 10 month-old kidney (0 65 mg /kg) and in the 2 year-old (2 75 mg /kg) but not in the 7 week old *one* The essential metals were found in distributions and concentrations similar to those of adults Manganese was if anything more concentrated zinc less so while copper was comparable showing an affinity for liver Molybdenum was in all livers while cobalt was present in only two

Within the limits of these observations, and in view of what is known the following further conclusions can be drawn 1 Titanium nickel and cadmium are not essential to infant life but accumulate with age 2 Aluminum chromium silver and lead either qualify as essential trace metals or pass through the placental membrane Obviously titanium nickel cadmium and tin do not so pass

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Some of these metals accumulate with age in Americans others do not In Table XXII Chapter V are shown examples Obviously cadmium titanium nickel and tin in all tissues and aluminum in lung increase from little or none in infants to relatively higher concentrations at older ages The striking examples are in cadmium and titanium

Trace Metals in Tissues from Uncivilized People In order to ascertain more definitely what trace metals are essential and what are not a small number of tissues from African natives in little contact with Western Civilization were obtained by Dr Perry from Uganda and analyzed by Dr Tipton (266) The ages ranged from 18 months to over 50 years there were three under 10 and four over 40 None showed any evidence of atherosclerosis in the aorta or elsewhere even fatty streaks were not seen The causes of death were several 6 patients died of acute infections No age trends in essential metals were apparent as is the case with Americans The interesting findings lay in the absence of those which might be guessed to be products of Western Civilization cadmium (in only one kidney) nickel and tin and the much smaller amounts of silver lead chromium and possibly titanium (Table XXXVII)

Conclusions Therefore it becomes apparent that nickel chromium cadmium lead silver and tin are not essential elements but results of civilization a conclusion which could be drawn from the analyses of children s tissues only for cadmium nickel and titanium The possibility of these six elements found in American tissues being toxic must therefore be considered Common sense excludes silver because of its low concentrations In addition we cannot rule out the possible essential nature of aluminium barium strontium and for lung of vanadium and ti

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Are these extraneous elements biologically active or inert? Could one or more of these abnormal elements displace an essential metal and thus lead to metalloenzyme inhibition or combine with sulfhydryl enzymes and so inactivate them (Table XXVIII)? If so the possibility of inhibition causing dysfunction leading to disease is considerable

METALS OF POSSIBLE BIOLOGICAL SIGNIFICANCE IN THE FIRST TRANSITIONAL GROUP

It is interesting that the transitional and nearby metals in the periodic table are those with *most biological* activity an expression perhaps of their structures (267) Other than the known essential trace metals of the first transitional group four might serve in metalloenzymes but have at present no known function i e titanium vanadium chromium and nickel Vanadium is found in all of the animal phyla is concentrated from *sea water by* tunicates as an essential oxygen carrier (268) is required by aspergillus niger (269) is concentrated in certain *mush*rooms (270) --

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Evidence for Vanadium Being an Essential Trace Metal What evidence there is for vanadium being essential to mammalian metabolism is indirect but good Aside from its use by ascidia which use it for oxidation reduction reactions at a time when they are buried in mud petroleum contains varying amounts of vanadium in a porphyrin form which has led to the hypothesis that animal organ isms and not plants originated the formation of petro- leum It is found in mammalian tissues at a fairly good concentration said to be 0 13 per cent dry weight 1 2 mg /kg for invertebrates and 0 1 mg /kg dry tissue for vertebrates (268) While its occurrence may be a chance contamination universal presence and three valence states (V^{+++} V^{++++} V^{+++++}) with an ability to release energy similar to phosphorus make it likely that vanadium may be essen tial Tipton found it only in the lung

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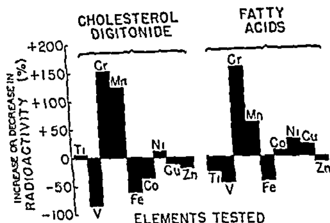


FIG 18 The effect of certain transition metal salts on the incorporation of C^{14}-carboxyl labeled acetate into cholesterol and fatty acids by surviving rat liver (From Curran G L. *J Biol Chem* 210 765 1954)

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Normal urine contained less than 0 05 to 1 03 γ/L (mean <0 46) hypertensive urine less than 0 05 to 4 4 γ/L (mean 0 88) Treatment did not change the means significantly (0 67 to 0 71 γ/L) nor did hydralazine or EDTA cause a consistent loss

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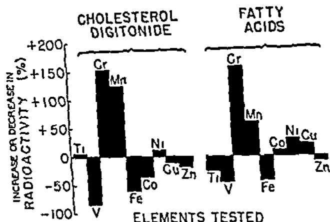


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Scandium and gallium are found in soils. The traces of gallium in human lungs probably have been inhaled since gallium is present in all aluminum minerals Both are relatively unreactive compounds with only one valence state

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Lead There is lead in all human tissues at birth and during life This toxic metal accumulates especially in bone and liver As far as is known it is not an essential constituent of any living organism getting into food mainly from the use of its compounds on plants and from vessels in which food is manufactured transported or stored Shell fish may absorb lead from sea water contaminated with drainage from factories and animals from sprayed plants African tissues had little

A knowledge of the coordination number of a metal the shape of its chelate and its periodic group allows a reasonably accurate if indirect method of predicting displacement of a known essential metal and in activation of its enzyme Conversely by inactivation studies unknown

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As in the case of zinc and lead cadmium can be dissolved in slightly acidic media Therefore foods and waters coming in contact with cadmium could become contaminated by traces There are three possible sources 1) Water is usually piped in American houses through galvanized zinc coated iron pipes If soft aerated in muncipal water stations to contain carbon dioxide and chlorinated appreciable quantities of zinc lead and presumably cadmium could be dissolved from the galvanized coat If hard however insoluble carbonates are laid down on the coating protecting it from solution and corrosion Water softeners probably would not soften water enough to corrode zinc Chlorinated water even when hard takes up zinc.* 2) Carbonated beverages are acidic and will take up zinc lead and presumably cadmium from galvanized or zinc lined

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Cardiovascular Implications Aluminum and strontium were present in all samples of American heart muscle These metals plus lead and tin were found in all aortas In kidney there was the additional metal cadmium in liver these five and silver In adrenals were the same six and

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A logical therapeutic regimen within the limits of pres ent-day vision is a concerted effort at removal by relatively nonspecific chelators followed by replacement of essential metals so removed Generalized deficiency states of the essential metals iron cobalt copper and molybdenum is probably unlikely under such a regimen manganese and zinc may require replacement Too much of an essential metal however probably can cause as much disorder as too little When deficiencies are recognized they can be treated

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Chapter VII

SOME MECHANISMS IN ATHEROSCLEROSIS

INTRODUCTION

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Atherosclerosis can occur without diastolic hypertension Severe degrees of the disease in the aorta causing loss of elasticity produce systolic hypertension because the pipes are hard but do not of themselves cause elevated diastolic pressure Contrariwise hypertension can persist without significant atherosclerosis especially in China (8 313 440)

In 1941 Snapper made some pertinent comments which are lately being appreciated (8) Another point which must be specially mentioned is the infrequency of arteriosclerosis in North China The rarity of arteriosclerosis is proved by the scores of middle aged patients dying from all sorts of diseases showing hardly any sclerosis at autopsy Extensive arteriosclerosis certainly does occur in North China but the thickened inelastic aorta with the widely

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PATHOGENETIC FACTORS

According to Friedman *et al* (314) the following schema invokes the multiple etiological factors and illustrates the pathogenesis of atherosclerosis

Time	×	Intrinsic (?) Intimal Derangement	×	Quantitative and Qualitative Alteration of Plasma Lipids Including Cholesterol	×	Blood Pressure	= Atherosclerosis

We will consider each of these factors separately

1 Blood Pressure Rarely does long standing diastolic hypertension in Caucasians exist beyond the age of 40 without atherosclerotic lesions being found in aorta major arteries or coronaries Experimental hypertension is necessary to induce atherosclerosis in the rat a resistant animal and is desirable in the dog Fat in serum can be made to ✓infiltrate the walls of arteries under high pressure especially if the intima is injured (315) Even in normotensive persons lesions develop at the sites of changes of pressure such as the mouths of the renal arteries in the Circle of Willis and at the bifurcation of the aorta (316 317) Atherosclerotic gangrene seldom occurs in the arm but is frequent in the leg where the hydrostatic pressure of the blood in the upright position is added to the blood pressure (318) These lesions are believed to be the result of pressure causing deposition of insoluble cholesterol or its esters subintimally either by forcing them into the vessel walls or preventing their diffusion out after entrance via the vaso vasorum

2 Intimal Injury Mechanical injury to the intima of dogs results in the formation of atheromata (320 322) It is difficult to understand how injury can occur at a normal pressure although acute hypertension in animals (323)

PATHOGENETIC FACTORS

According to Friedman *et al* (314) the following schema invokes the multiple etiological factors and illustrates the pathogenesis of atherosclerosis

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metal interference (with decarboxylases for example) that in liver by marginal concentration of vitamin B_6 excessive saturated fatty acid load and possibly metals There is no evidence for a generalized deficiency state except for the high incidence of dandruff in the population believed by some to be dependent upon vitamin B_6 and fatty acid imbalance

3 Trace Metals The synthesis of cholesterol and fatty acids by surviving rat liver can be influenced by metals of the first transitional group (Fig 18) Chromium and manganese have a pronounced enhancing action vanadium a depressant one (248) Vanadium also promotes unsaturation of phospholipid fatty acid and oxidation of the double bond opposed by manganese (Table XXXVIII) There is no evidence however that chromium is implicated in the hypertensive process In American tissues hepatic chromium is much less concentrated than manganese a known lipotropic agent (231 259) (Chapter VI) Many metals directly affect oxidation of unsaturated fatty acids *in vitro* Hydrogenation to harden or saturate them is accomplished commercially mainly by copper and nickel sizeable quantities enter the fat during processing (256) Cadmium however inhibits at least one vitamin B_6 enzyme DOPA decarboxylase (Chapter V) although it does not affect hepatic synthesis of cholesterol in the rat (331) Obviously we need to know much more about the effects of abnormal metals on the enzymes concerned in fatty acid and steroid synthesis

A significant series of experiments were done by Curran and Costello in rabbits (280) Hypercholesterolemia was induced by feeding cholesterol at the 3 per cent level for 4 weeks On resumption of a normal diet cholesterol levels usually fall slowly Half the rabbits were fed vanadium as $VOSO_4$ (0 05 per cent) for 6 weeks There were

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examine the possibilities we can look at factors of suspicious import in hypertension which could conceivably influence the development of cholesterol-containing atherosclerotic plaques in arteries

There is no good evidence that the blood cholesterol is higher in American hypertensive than in normotensive people Therefore the increase in the rate of progression of atherosclerosis in hypertension is probably largely due to intravascular filtration pressure causing deposition of lipids through the intima (319)

Hypertension and atherosclerosis however may be interrelated in a more fundamental fashion than by mechanical excessive filtration of cholesterol through intima by the high pressure when there are adequate cholesterol levels in blood 1) A conditioned vitamin B_6 deficiency may involve both disorders 2) abnormal trace metals may not only affect the hypertensive process but increase cholestrol synthesis At this point the reader may wonder whether or not the author has an obsession with vitamin B_6 and its functions Upon careful thinking in terms of enzymatic mechanisms this coenzyme continually obtrudes itself into possible schemata derived from experimental and clinical data both in hypertension and in fatty acid metabolism

We must turn to epidemiologic data for evidence that there is no common denominator of these two diseases Some atherosclerosis but no hypertension has been found in Alaskan Esquimaux (332) the incidence may be smaller than in whites Hypertension is extremely common in Hawaiian sugar plantation workers as is atherosclerosis but severe coronary sclerosis is less frequent than in Caucasians (333) Atherosclerosis is said to be prevalent in Kirghiz nomads as is contracted kidney (from hypertension?) (334) Snapper observed hypertension but little

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Comment Some derangement common to both diseases may be present but atherosclerosis with which the American public is riddled is more frequent in the population than is hypertension Therefore while atherosclerosis can and does occur without hypertension the contrary is unusual in our civilization but frequent in others Both abnormal trace metals and local pyridoxal deficiency may be implicated

THE ROLE OF FAT AND OTHER LIPIDS

Let us review modern ideas on the pathogenesis of the lesions other than the factors already discussed Most of the recent interest in the subject has centered on fats Quite a case can be made for the role of cholesterol which is largely carried by lipoproteins as a strong link in the chain of reactions leading to the formation of plaques the subject has had its ups and downs since 1914 but probably is here to stay As Aschoff so aptly put it From plasma of low cholesterol content no deposition of lipoids will occur even *though* the mechanical conditions are favorable (327)

Normal Cholesterol Levels in Blood What is the normal level of blood cholesterol? That is a difficult question to answer The levels found in Europeans and especially Americans may not represent normal *values* but rather average values in a population subject to the disease If so we should look elsewhere at healthy adults to determine our normal standards and thus our therapeutic aims in controlling and reversing the atherogenic tendencies of

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the populations with high values Just because a disease is common does not make it or any one of its measurable parameters normal

Considerable information comes from studies in other than Western countries (Table XXXIX) If these values for blood cholesterol be correct as there is little reason to doubt, the normal range is 120 to 160 mg per cent higher values may be ascribed to dietary influences or their concomitants That environment and an increasing standard of living may affect blood lipids was well shown by Toor *et al* in their study of recent immigrants to Israel compared to immigrants living 20 years or more in that country (338) (Table XL)

In Table XLI are shown some wide variations in total cholesterol and other lipids in blood done by analytic methods which are considered quite accurate from various Western countries The variations are unexplained Page *et al* tried to check the differences between their analyses done in New York (339) and Boyd s done in Ontario (340) they state our results for cholesterol determined in the presence of the other lipids are likely to be low rather than high For the fact that our normal cholesterol values range so much higher than those of Boyd (in Ontario) and of Gardner and Gainsborough (in England) we therefore lack an explanation We can find no source of error for our results and none is obvious for theirs" Since Boyd s normal subjects were taking the standard high fat diet customary in this country (340) it is possible that an en vironmental factor not present in England and Ontario but influencing levels in New York was operating

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VARIATIONS OF PLASMA CHOLESTEROL LEVELS IN WESTERN COUNTRIES*

Author	*Location*	*Date*	*Total*	*Free*	*Phospholipids*
Gardner and Gainsborough	England	1927	153 ♀ 169 ♂	54 50	
Man and Peters	Connecticut	1933	207♂		222
Boyd	Ontario	1935	177♂	52	185
Page *et al*	New York	1935	232♂	82	181
Peters and Man	Connecticut	1943	194	54	240
Gertler and Garn	New York	1950	224		299
Gubner and Ungerleider	New York	1949	211		
Keys	Minnesota	1949	218		
Kornerup	Denmark	1950	203	55	172
Block *et al*	Minnesota	1951	181		234
Perry and Schroeder (Hypertensive)	St Louis	1955	226		

NOTE The earlier determinations were done by digitonide precipitation and the later usually by acetic anhydride which tends to give lower values (439)

*From Page *et al* (339) and Katz and Stamler (356)

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acid esters of cholesterol regardless of the length of the carbon chain melt at higher than body temperatures the lowest is for oleate (44 5°C) and linoleate (42°C) compare stearate (82 5°C) and palmitate (90°C) (348) Therefore variations in solubility and melting point may determine deposition of these esters in the lesions Solubilities of the cholesterol esters of β-lipoproteins believed to be of atherogenic importance (350) are not known

Since pyridoxal is concerned with hepatic desaturation of di and tri unsaturated fatty acids to tetra and hexa forms (349) this coenzyme could influence the type of ester Experiments in our laboratories however have failed to show that vitamin B_6 raises the iodine number of plasma lipids when given for a week or 10 days the tendency was for it to fall (Table XLII) Surprisingly enough the iodine numbers of blood lipids was found to be much higher in Chinese (8) than in American patients (Table XLIII) probably a reflection of their high unsaturated fatty acid diets

Other Lipid Substances We have not considered the phospholipids of plasma nor the chylomicrons containing neutral fat nor the lipoprotein fractions which carry cholesterol These are complicating parameters whose significance is unclear Their relations are shown in Table XLIV Keys has said At the present time (1951) it is entirely unjustified to attribute to G measurements any special virtues beyond that for simple cholesterol measurements for the prediction of atherosclerosis or the estimation of the activity of the atherosclerotic process (351) The type of lipoprotein its solubility and its physical characteristics however may have atherogenic properties These large molecules transport lipids and steroids in blood (352) Therefore an increase in β-lipoproteins may do something to the process directly or indirectly but at

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IODINE NUMBERS OF SERUM LIPIDS WHITE PATIENTS

Patient	Age	Sex	Total Cholesterol mg /100 ml	I_2 No	Atherosclerosis Diagnosed	
T K	64	♀	96	71	+	Lobar pneumonia convalescent
P M	65	♂	101	94	+	Pulmonary insufficiency bronchiectasis
F I	59	♂	106	56	+	Rheumatic heart disease
M S	54	♂	111	70	+	Myocardial infarction
L J	68	♂	119	82	+	Myocardial infarction
J D	67	♂	124	89		Prostatic hypertrophy emphysema
W D	62	♀	131	63		Hyperthyroidism
R S	68	♂	133	97	+	Metastatic carcinoma of stomach
K S	49	♂	134	61	+	Inferior vena caval *obstruction*
B H	67	♂	148	70	+	Cerebral thrombosis
M J	50	♂	182	124	+	Pulmonary fibrosis and insufficiency
F S	55	♂	191	61	+	Hypertension
G B	58	♂	206	78	+	Hypertension
I S	48	♀	210	88	+	Angina pectoris
T B	74	♀	231	126	+	Metastatic carcinoma of breast
G H	45	♂	242	73	+	Angina pectoris
J M	*60*	♀	550	162		Nephrotic syndrome
I T	44	♂	>500	*102*		Amyloidosis nephrotic syndrome
J B	65	♀		84	+	Cerebral thrombosis hypertension
M C	53	♀		76		Vascular tumor of brain
J H	54	♂		70	+	Hypertension aneurysm *of* Circle of Willis
A H	63	♀		62		Chronic cystitis
V V	74	♂		76	+	Diabetes Parkinsonism
O W	70	♂		78	+	Carcinoma of prostate
Mean	60			81		

From data of Ferry Schwartz Hager and Schroeder

NOTE The iodine number *of human depot fat is* 64 (348) and cholesterol is 65 8 The *mean* iodine number *of* fatty acids in plasma of normal Chinese *is* 156 6 (8)

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in the blood What they are and what they are made of is of the greatest importance

The lipoproteins carry steroid hormones cholesterol and its esters, carotene or vitamin A α tocopherol and acetal lipid (containing hydroxyl groups) (352 353 387) Most (75 per cent) of the free cholesterol in serum is in the β-lipoprotein fraction as is the esterified fraction (73 per cent) while less (55 per cent) of the phosphorus is in this fraction Barr found somewhat lower values in β-lipoproteins (354, 355) Thus increase in the cholesterol phospholipid ratio suspected to be of atherogenic significance means in terms of lipoproteins that with relatively less phospholipid than cholesterol the β-lipoprotein fraction will be increased in the proportion of 1 1 35 Gofman finds that particles of the S_f 10 20 classes have weight ratios of cholesterol to phospholipid as high as 1 1 3 (356)

Exogenous Cholesterol There is no evidence that a *diet* containing reasonable amounts of cholesterol (up to *1 0 Gm* per day or the equivalent of four eggs) influences the level of blood cholesterol (357) Feeding healthy volunteers (358) or patients (359) up to ten times that amount causes insignificant changes in plasma levels * Actually at 200 mg per 100 ml blood there is about 8 Gm in circulation with an additional *3 to 4 Gm in liver* and a considerable amount in other *tissues While* exogenous cholesterol probably little affects plasma levels *in man* the reverse i e restricting the dietary *intake* to very low values *does* decrease plasma levels since all dietary cholesterol is contained in *fatty foods* which therefore need

*It is possible to block some of the intestinal absorption of exogenous cholesterol by plant sterols *such a s os erol* in large doses The effect on plasma cholesterol however is either insignificant, or significant to a very minor degree

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There are three habits largely common to the U S A and some European countries which tend to raise the dietary intake of saturated fats (202 348 360) 1) Since 1920 animals fattened for slaughter have been fed high carbohydrate diets in order to lay down a hard fat Meat from animals eating unsaturated vegetable fats is oily and housewives do not like to buy it the melting point is low 2) For many years vegetable fats (unsaturated) have been commercially hardened often by a copper or nickel catalyst in order to provide shortenings or margarine which are solid at room temperatures 3) The consumption of milk butter and cheese has increased milk fats contain shorter chain saturated fatty acids and are believed to be atherogenic (356)

Relation of Dietary Fats to Cholesterol Why does an excessive intake of hard or saturated fats cause atherosclerosis? The following information is known

1 Animals lay down in their tissues part of the fat ingested This has been demonstrated in all mammals but man Pigs fed very long chain high melting point fatty acids may crack in the cold Unnatural fats (odd numbered carbon atoms or optical isomers of natural fats) can be recovered from the bodies of animals to which they are fed in amounts from 10 to 25 per cent (348)

2 Cholesterol esters can be formed of the type of fat in the diet Thus stearic or even unnatural fatty acid esters of cholesterol can be recovered when a specific fat is fed (348)

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There are three habits largely common to the U S A and some European countries which tend to raise the dietary intake of saturated fats (202 348 360) 1) Since 1920 animals fattened for slaughter have been fed high carbohydrate diets in order to lay down a hard fat Meat from animals eating unsaturated vegetable fats is oily and housewives do not like to buy it the melting point is low 2) For many years vegetable fats (unsaturated) have been commercially hardened often by a copper or nickel cata lyst in order to provide shortenings or margarine which are solid at room temperatures 3) The consumption of milk butter and cheese has increased milk fats contain shorter chain saturated fatty acids and are believed to be atherogenic (356)

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TABLE XLV

COMPOSITIONS OF CORN COTTONSEED OLIVE OILS AND BUTTER*

	Corn	*Cottonseed*	*Olive*	*Butter*
Iodine number	103–129	90–110	79–90	26–38
Saturated acids (%)	12–18	21–32	9–19	30–43
Oleate	21–49	19–36	64–86	28–41
Linoleate	34–61	34–56	4–15	
Linolenate	0–2 9	0	0	0
Arachidonate	0	0	0	0
Squalene (mg %)	28	8	383	0
Ergosterol	+	+	0	+
Sitosterol	+	+	0	
Stigmasterol	+			
Rate of enzymic hydrolysis	1	2	3	
Tocopherol (mg %)	87–250	83–110	3–30	

* After Deuel (348) and Eckey (447) Contents vary with climate soil and seed

cholesterol has been shown to be squalene a hydrocarbon with six double bonds having the empirical formula $C_{30}H_{50}$ (362) Squalene is found in the unsaponifiable fraction of several but not all fish oils and only one plant oil olive oil (0 41 0 54 per cent) Other vegetable oils contain only very small amounts (peanut oil 0 07 per cent) Animals fed labelled squalene synthesize cholesterol 50 times as efficiently as when given labelled acetate (362) Squalene is not converted to fatty acids as is acetate Another precursor of cholesterol is provitamin D_3 or 7-dehydrocholesterol widespread in foods but in small quantities

Effect of Various Fats on Blood Cholesterol Levels in Man One can gain some information on the relationship of the type of fat ingested to the level of cholesterol in plasma by human experiments in which dietary fat was markedly increased (Table XLVI) If these results are valid an examination of the table points at once to specific dietary factors or the lack of them which alter cholesterol

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XLVII) Arachidonic acid a normal component of animal tissues lecithins cephalin phosphatides and fats is an other essential fatty acid formed from linoleic probably by a vitamin B_6 enzyme system (349)

Therefore the factor in certain vegetable fats (and not others) which lowers blood cholesterol may not lie in the presence or absence of unsaturated fatty acids themselves

TABLE XLVII

ESSENTIAL FATTY ACID CONTENT OF SOME EDIBLE OILS (%)

Food	*Linoleic*	*Linolenic*	*Production*†
Linseed	15–43	40–53	2 2
Peanut	47–72	0	3 9
Sunflower	44–75	0 1	2 0
Sesame	40–48	0	1 5
Soy bean	52 0	2 3–11	3 8
Coconut	1–2	0	4 6
Animal fats	+	0	17 8
Rapeseed	12–16	7–10	3.3
Palm	6–11	0	3.3

* After Eckey (447) †Estimated World 1951 billions of lbs

but in the linolenic or other specific fatty acid content The cholesterol lowering diets of Kinsell *et al* contain nuts in large amounts (363) The fat from some nuts especially walnuts contains linoleic and linolenic acids (348) In this respect Kinsell s diets (364 365) contained soybeans soy lecithins soy sauce corn oil and walnuts all containing linolenic acid while this fatty acid has not been found in peanuts almonds and cashew nuts (348) The hydrogenated oils in margarine Crisco and peanut butter as well as cottonseed peanut and olive oil which apparently do not contain linolenate were also given in spite of these fats at least two of which usually raise blood cholesterol it fell Brain extract probably cephalin which

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Pyridoxal and Trace Metals The amount of vitamin B_6 in the diet has a definite influence on essential fatty acid metabolism in animals Vitamin B_6 deficiency and essential fatty acid deficiency in rats resemble each other grossly and each factor will partly alleviate the other There are however fundamental differences in enzymes in the two

TABLE XLIX

Comparison of Essential Fatty Acid and Pyridoxine Deficiencies in Rats (384)

Function	*Organ*	*Essential Fatty Acid*	*Pyridoxine*
Respiration	Liver	Increased	
Cytochrome oxidase	Liver	Increased	Increased ±
Succinic oxidase	Liver	No Change	No Change
Phosphate esterification	Liver	Decreased	Decreased
Glutamic dehydrogenase	Liver	Decreased	Decreased
Butyric dehydrogenase	Liver	Decreased	No Change
Succinic dehydrogenase	Liver	Decreased	No Change
Glutamic decarboxylase	Brain	—	Decreased
Arachidonic synthesis	Carcass	Decreased	Decreased
Hexaenoic synthesis	Carcass	Decreased	Decreased
Octanoate oxidation	Carcass	—	Decreased

conditions (Table XLIX) Apparently vitamin B_6 is essential for desaturating partly unsaturated fatty acids such as linoleic further to synthesize arachidonic and in metabolizing linolenic to hexaenoic acids Linoleic is a precursor of arachidonic and linolenic of the hexaenoic acids (349)

deficiency or saturated fatty acid excess Thus the members of the Russian Orthodox Church eat nothing of animal origin during Lent Advent and on Wednesdays and Fridays *and use oils high* in linolenic acid Roman Catholics by custom supply themselves with adequate essential fatty acids on Fridays and during Lent but do not restrict other animal fats Mohammedans have strict dietary laws *during* Ramadan In terms of deposition of lipid these religious habits probably do no harm in maintaining or restoring the integrity of the intima.

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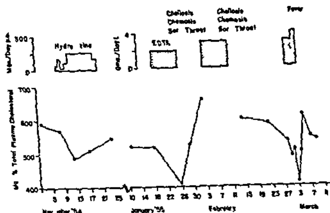


FIG 20 Effects of oral hydralazine and intravenous EDTA on plasma cholesterol levels L. T 44 years of age was seen in October 1954 because of mild exertional dyspnea and ankle edema for six months At 7 years of age he had Marie Strumpell arthritis and at 25 years of age migratory polyarthritis without urinary symptoms Nephrosis was clinically evident and amyloidosis was proved by renal punch biopsy To lower his plasma cholesterol hydralazine was begun without evident clinical improvement. In a further effort to lower his plasma cholesterol three courses of parenteral EDTA were given On the sixth day of this first course of therapy slight inflammation of the mucous membranes and a magenta tongue were observed and he complained of soreness about his mouth and gums By the final day cheilosis chemosis scrotal inflammation and pustular lesions over the face and trunk had appeared Within a week the lesions had vanished and a second course of EDTA was begun On the fourth day stomatitis reappeared and within 7 days the same syndrome was present again necessitating the discontinuation of therapy The 3-day final course produced no such lesions however fever immediately followed the dosage increase to 4 Gm. Cholesterol values for the second course were not plotted because such a low plasma level was attained that a laboratory error was suspected (303 mg per 100 ml on a single determination) The changes in cholesterol preceded clinical toxicity (From Perry H M Jr and Schroeder H A J Chronic Dis 2 520 1955) Metal excretion in Table XXX p 160

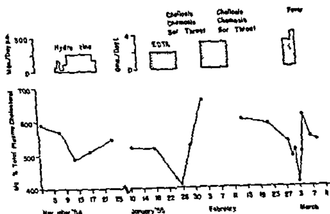


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There appears to be something in certain but not all vegetable fats which lowers blood cholesterol markedly in man while animal fats hydrogenated vegetable fats and other vegetable fats with a lower iodine number raise plasma cholesterol As a first guess this substance may be linolenate an essential fatty acid If that is so Europeans and Americans may be suffering from a relative essential

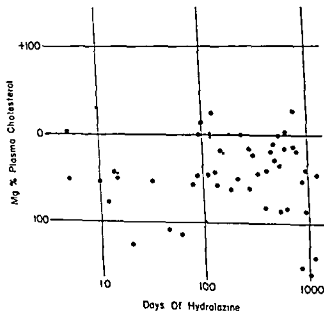


FIG 92 Effect of oral hydralazine on total fasting plasma cholesterol in 119 hypertensive patients. Changes in cholesterol concentrations before and after hydralazine are plotted against the length of therapy Each large dot indicates a patient with an initial cholesterol level of more than 215 mg per 100 ml plasma. Each small circle indicates a patient with lower initial values below 211 mg per 100 ml plasma (From Perry H M Jr., and Schroeder H A *J Chronic Dis* 2 590 1955)

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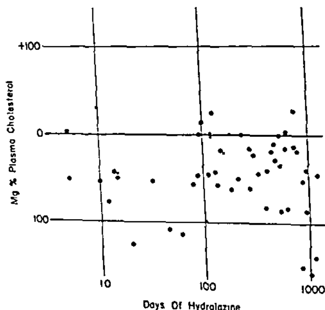


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The nature of the vitamin B_6 deficiency and its possible relation to trace metals has already been discussed The plasma lipids under consideration include a) Cholesterol esters which are said to be usually of unsaturated fatty acids although esters of equal length saturated fatty acids are lighter and more insoluble Dietary excess of the latter could influence their nature b) Lipoproteins or protein fatty acid complexes the nature of which are unknown The saturated fatty acid esters should be lighter and more insoluble than their unsaturated counterparts If so they should centrifuge more slowly (or float more rapidly) A lipoprotein with a specific flotation rate of S_f 0 10 if its fatty acid became saturated should theoretically change to the S_f 10 20 class unless rearrangement of the molecule took place c) Phospholipids the fatty acid components of which depend partly perhaps on dietary intake but usually are formed of unsaturated fatty acids in functioning tissue (brain and liver)

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In this chapter we have spoken of trace metal imbalances conditioned vitamin B_6 deficiencies and essential fatty acid deficiencies We have emphasized that these deficiencies are relative conditioned and local to one or at most a few enzyme systems There is no practical way however of reversing vitamin B_6 deficiencies at the present time The administration of 50 mg of pyridoxal hydrochloride daily to many patients has not resulted in a detectable fall in blood cholesterol The administration of at least two trace metals cobalt and manganese in large daily doses have not caused clinical changes detectable by ordinary laboratory methods Only by chelating agents have we been able to affect blood levels favorably (180)

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4 Diastolic normotension must be achieved and maintained whenever possible A compromise is hazardous merely modifies the disease promotes drug tolerance and does not allow eventual reduction of dosage

5 The use of any ganglionic blocking agent the action of which does not last for 24 hours requires that blood pressure be measured before each dose in order to prevent a) hypertension b) hypotension and c) to provide as constant a blood level as possible throughout the day and night Varying requirements and absorption necessitate varying dosages according to the prevailing levels of blood pressure

6 Arterial hypertension due to increased generalized vasospasm is a disorder or a disease The patient either has it or has not If he has severity varies widely from slight to marked Therapy should be applied when both patient and physician want to control the disease If therapy is not applied the responsibility rests on the physician that the disease is not doing or going to do harm

EVALUATION OF PATIENT FOR DRUG THERAPY

The first question to be answered is Has the patient hypertension? A diastolic pressure of 90 mm Hg or over (measured by the disappearance of Korotkoff sounds) is strongly suggestive in fact usually indicative of generalized vasospasm in the absence of tachycardia polycythemia or coarctation of the aorta When persistent it suggests chronic hypertension when relieved by relaxation it suggests the prehypertensive state

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Renal status is evaluated most easily by routine urinalysis and the intravenous injection of phenol red (PSP) with urine specimens obtained 15 30 and 60 minutes after injection The test is simple and reliable The bladder need not be emptied before the test although the first specimen may show a somewhat smaller amount of PSP * for unknown reasons (Reabsorption of PSP by bladder wall has not been ruled out) Adequate hydration is essential for accurate values The urinary concentration test is impractical on an outpatient basis owing to difficulties in restricting the amount of dietary water If the 15-minute PSP excretion is less than 10 to 15 per cent azotemia may be suspected

Retinoscopy is essential in all cases The appearance of exudative or hemorrhagic *retinitis* is often a poor prognostic sign making treatment mandatory The best method for grading fundal changes is that of Keith and Wagener

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* In a series of 39 medical students paired for the test with bladder empty the 15-minute excretion was 3?.5 per cent with bladder full, 30 9 per cent The normal values with bladder initially empty were 1? minutes 3?.5 per cent 30 minutes 21.2 per cent 60 minutes 17.0 per cent with a total of 73 7 per cent

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   b Aneurysms*
6 Diminution of the calibre of the renal arteries
   a Congenital malformations hypoplasia*
   b Atherosclerosis, with atheroma of the main renal artery (common)*
7 Disorders of the urinary tract
   a. Obstructive disorders
      (1) Lithiasis*
      (2) Hydronephrosis (*usually infected*)*
      (3) Pyonephrosis
      (4) Congenital malformations*
      (5) Prostatic hypertrophy*
      (6) Uterine prolapse
      (7) Pelvic tumors (fibromyomata)*
   b Pyelonephritis (common)*
8 Venous obstruction
   a External compression of renal vein
   b Congestive heart failure*

The following intrarenal diseases must be considered
1 Inflammatory vascular lesions
   a Disseminated lupus erythematosus*
   b Polyarteritis nodosa*
   c. Syphilis
   d Thromboangiitis obliterans
2 Inflammatory renal lesions
   a Glomerulonephritis*

The following endocrine diseases can influence hypertension
1 Hypophyseal tumors and hyperfunction*
2 Adrenal cortical and medullary tumors and hyperplasia*

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    (3) Pyonephrosis
    (4) Congenital malformations*
    (5) Prostatic hypertrophy*
    (6) *Uterine prolapse*
    (7) Pelvic tumors (fibromyomata)*
  b Pyelonephritis (common)*
8 Venous obstruction
  a External compression of renal vein
  b Congestive heart failure*

The following intrarenal diseases must be considered
1 Inflammatory vascular lesions
  a Disseminated lupus erythematosus*
  b Polyarteritis nodosa*
  c. Syphilis
  d Thromboangiitis obliterans
2 Inflammatory renal lesions
  a Glomerulonephritis*

The following endocrine diseases can influence hyper tension
1 Hypophyseal tumors and hyperfunction*
2 Adrenal cortical and medullary tumors and hyper plasia*

EVALUATION OF GENERALIZED VASOSPASM IN HYPERTENSIVE STATES

It is of little more than academic interest what the underlying pathogenetic factors in a state of severe hypertension may be except when chronic pyelonephritis can be treated with antibiotics (often with little success) or recurrences of glomerulonephritis prevented by antibiotics designed to abort upper respiratory tract infections It also matters little what the type of renal disease contributing to the vasospasm may be pyelonephritis glomerulonephritis secondary arteriolar nephrosclerosis or even polycystic disease What do matter are the relative influences of neurogenic nephrogenic or adrenocortical factors in causing the vasospasm for the relative amounts of different drugs required will differ according to the amount of renal ischemia present Therefore it is a good plan to group cases according to several stages of the disease dependent upon the amount of vasospasm one finds and its lability

The degree of lability of the vasospasm is the factor *which* determines these stages Complications such as cerebral vascular accident and coronary arterial occlusion can occur in any stage mild severe or normotensive as they are *caused not* directly by vasospasm but by an associated disease atherosclerosis The *fact that this* other disease can be influenced by the *severity of the hypertension* i e the vasospasm has little to do with therapeutic measures aimed at *vasospasm* Therefore classifications based partly upon atherosclerotic damage are valid for purposes other than the choice of drugs or procedures such as prognostic implications and for surgical risk One would not use the most potent drugs in a patient with hemiplegia or congestive heart failure who exhibited severe atherosclerosis and *mild* hypertension one would use them however in a patient with severe but *asympto-*

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Serious secondary atherosclerotic complications may or may not be present if so about 30 to 40 per cent may be dead in 3 years The ocular fundi are Grade I or II renal function is normal or nearly normal and the blood pressure is roughly 180/100 to 220/120 mm Hg during rest in bed Reserpine plus fairly large doses of hydralazine (300 to 400 mg per day) will control about half of these cases eventually the remainder require the addition of ganglionic blockade With time individuals in this stage uniformly exhibit reversal of the process and marked reduction of dosage in 2 to 3 years a majority can be maintained on reserpine alone and a few will be in a complete but probably temporary remission

Stage III is made up of individuals with Grade II to III (Keith Wagener) ocular fundi with or without occasional hemorrhagic and exudative lesions with severe generalized vasospasm and hypertension not relieved by heavy sedation (sodium amytal) Renal function is adequate but usually reduced Serious atherosclerotic complications may or may not be present. The blood pressure is usually 200/120 to 270/160 mm during rest in bed In this stage which usually carries a poor prognosis (40 per cent dead in 3 years) ganglionic blockade plus adequate doses of hydralazine (500 mg or more per day) are essential for control Reserpine may or may not be added mainly for its sedative action in smoothing out variations in blood pressure caused apparently by emotional lability in the presence of incomplete and irregular ganglionic blockade Therapeutic results are good 95 per cent surviving 5 years with considerable eventual reduction in dosages in most

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more theoretical benefits of dividing the dose or of using slowly absorbed increments such as are dispensed in some modern capsules than there is in dividing the dose of digitalis It has been our practice to use 1 0 mg per day for 1 month reducing it then to 0 5 mg and further reducing it to 0 25 or 0 1 mg slowly if excessive sedation appeared It is such a mild anti hypertensive drug in most cases that it should not be depended upon if signs of cardiovascular damage are present Its many side effects are listed in Chapter III nasal congestion being the most prominent and paranoid depression with suicidal tendencies the most dangerous This latter side effect places it among the agents indirectly hazardous to life the self satisfaction of a physician using it in severe and malignant stages who is afraid to employ more potent measures also makes it less directly hazardous At the first sign of increasing nervousness anxiety insomnia emotional tension and agitation it should be discontinued for agitated paranoid depression may develop (70 72) In our experience reserpine is not a very valuable agent for hypertension except as a curious kind of sedative with many side effects (Fig 24)

Reduction in dosage will often alleviate the usual depressive effects of the agent and may reduce the number of nightmares but nasal stuffiness can be most annoying Epistaxis induced by the drug usually necessitates discontinuation The time tested sedatives are the only alternatives to replace reserpine if it cannot be used

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1 Blood pressure is measured by competent nurses every 4 hours day and night and charted

2 Initial dose is given every 4 hours if the blood pres sure is above a chosen level usually 140 mm systolic It is not given if the blood pressure is below that level Slightly higher omit levels are used in the cases of atherosclerotic or azotemic patients 150 to 170 mm Hg Initial doses which are usually safe to give to patients with severe hypertension are Hexamethonium chloride 125 mg Pentolinium tartrate 20 mg Chlorisondamine 10 mg Mecamylamine 2 5 mg

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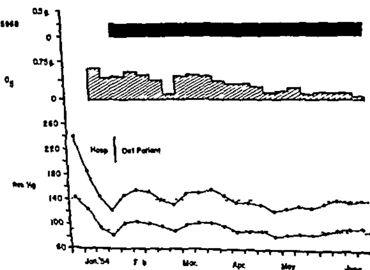


FIG 26 Examples of adequate control of blood pressure by giving adequate doses of ganglionic blocking agents (hatched area pentolinium bitartrate C_5) and hydralazine (solid black area 5968) In the case of H J in hospital control was poor at first until doses were raised sufficiently to achieve normotension. Each point represents the mean of six measurements Diastolic normotension was achieved. H O. Note increase in blocking agent requir d
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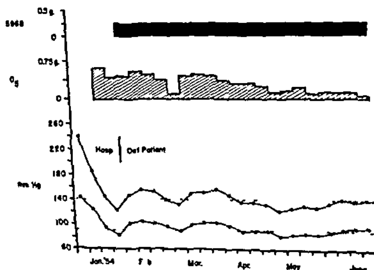


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Precautionary measures against obstruction of a hollow viscus already partially obstructed should be taken Abdominal scars prostatic hypertrophy, frequent rhinitis, are warning signs of possible trouble from this source They are usually less severe than the disease being treated When the drugs cannot be tolerated protoveratrine can be substituted with good results Surgical sympathectomy, of course does not carry this hazard Prostatic obstruction may require surgery

Use of Hydralazine This drug is given almost always in conjunction with either ganglionic blockade (Fig 28) or another milder agent acting on nerves (423) Because of initial side reactions mainly attributable to its antihistaminase action which are lessened with nerve acting drugs it is begun at doses of 25 mg every 4 hours raising the dose to 50 75 and 100 mg every 4 hours on 3 successive days It is given with the blocking agent Thus 500 mg a day is the usual dose in severe hypertension we have had to give as much as 1 0 Gm for short intervals These large doses may cause hydralazine disease in 10 per cent of patients after 6 months In general larger doses are given for greater nephrogenic components to the vasospasm smaller doses when the neurogenic component is large It is unreliable when used alone (189 396)

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Hydralazine disease appearing after 6 to 24 months of ingestion of fairly large doses necessitates two courses Stopping the offending agent entirely results in return of hypertension in these patients the mortality rate from hypertensive causes is 10 per cent Large doses of ganglionic and hypothalamic blocking agents with or without protoveratrine usually fail to control the hypertension adequately wide swings from high to low levels take place daily This situation is about the most difficult to meet in therapy and we have no solution Low salt diets or thiocyanate might be used sodium azide has been valueless (Fig 29) Closely related analogues of hydralazine have caused recurrences of the disease and chemically less related ones have been relatively worthless

Hazards of severe restriction of dietary salt are well known The nephrosclerotic kidney is a salt losing kidney to some extent and hyponatremia with renal failure (the low salt syndrome) can be induced by limiting the intake to a point less than obligatory urinary losses Borderline renal function predisposes to this usually fatal condition (397 399) (Fig 30)

The second choice involves marked reduction of the dose and the possible addition of cortisone until symptoms subside The disease resembles in part a phenomenon of depletion By small doses blood pressure can be controlled although L E preparations may remain positive the disease remain in a subclinical lupoid stage and

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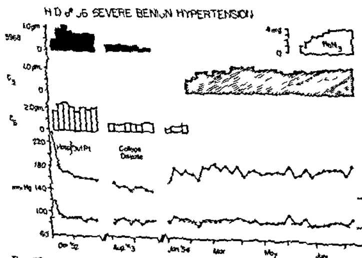


Fig 29 Examples of hydralazine (collagen) disease with special reference to blood pres

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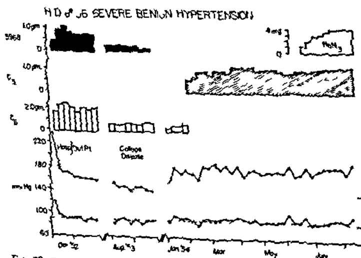


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Treatment of Crises In hypertensive crises (pulmonary edema cerebral edema toxemia of pregnancy) requiring parenteral administration two lines 20 mm apart are drawn across the graphic chart at the level at which systolic pressure is to be maintained After initial lowering of blood pressure by a small dose of a blocking agent blood pressure is measured every hour and a subcutaneous in jection of the full effective dose given if it is above the upper line half the dose if between the lines and none if below the bottom line Changes in total dosage must be made often The second day the two lines are drawn 20 mm lower Thus a patient with encephalopathy (wet brain) may have his pressure reduced from 300 mm Hg to 220 to 200 mm the first day 200 to 180 mm the second day and 180 to 160 mm the third day Usually oral medi cation becomes possible long before this time The pres sure must be reduced more drastically when there is pul monary edema We prefer parenteral ganglionic blocking agents to parenteral hydralazine because of their shorter

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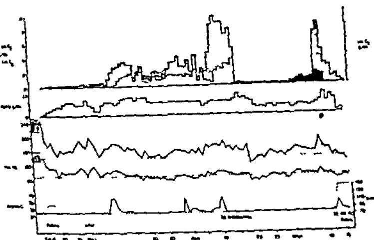


Fig 31 Medication and vital signs during hospitalization of a 52 year-old white male with malignant hypertension and pre treatment azotemia The upper bar graph indicates the daily dose of autonomic blocking agent. The open bars represent oral pentolinium tartrate (po C_5) The cross hatched bars represent parenteral pentolinium tartrate (im C_5) and the solid bars represent parenteral hexa methonium chloride (im C_6) The potency of oral pentolinium tar trate approximates that of intramuscular hexamethonium chloride however the scale for intramuscular pentolinium tartrate has been expanded to allow for its greater effect The lower bar graph indi cates oral hydralazine intake per day Daily blood pressure averages are shown each value being the mean of at least 6 and often as many as 24 readings taken with the patient in a sitting position The stippled area to the left indicates the pre treatment range of blood pressure The line graph at the bottom of the figure is a schematic representation of the vital signs The solid line shows the temperature in degrees centigrade which was below 37 5 except for three bouts of pyrexia The dotted line shows the pulse in beats per minute which was always below 80 except for two episodes of tachycardia The fig... values denote- high d Perry ... O'Neal K M and Thomas W A. *Am J Med* in Press 1957)

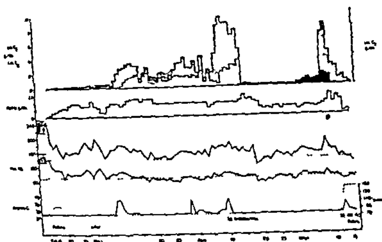


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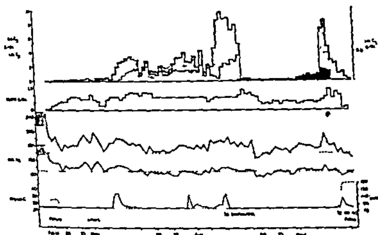


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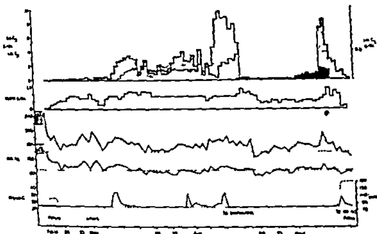
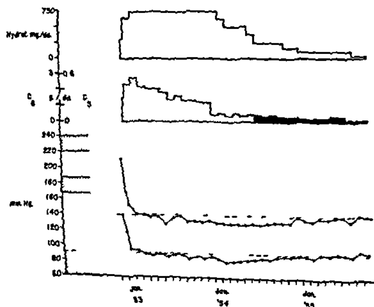


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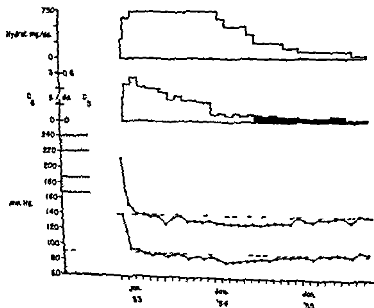


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The bar graphs indicate the drug intake the open area representing hydralazine the dotted hexamethonium (C_6) and the solid pentolinium (C_5) Note that the scale is different for the two methonium compounds since the second is approximately five times more potent than the first. (From Perry H M Jr and Schroeder H A. *Circulation* *13* 528 1956)

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1 b) Abnormal electrocardiographic patterns indicative of left ventricular strain revert to normal within several months Patterns suggestive of left ventricular hypertrophy revert to normal in some but not in all cases This may take 1 to 4 years Enlarged hearts often but not always become smaller in roentgenograms Time 1 to 5 years (406)

2 a) A few weeks after the start of therapy the progression of renal damage due to arteriolar nephrosclerosis is halted Unpredicted was a gradual return of depressed renal function in many but not all cases This occurs in from 1 to 4 years (405)

2 b) In from 1 to 6 weeks albuminuria diminishes or disappears When caused by pre-existing organic renal disease it remains at lessened quantities

2 c) In azotemic individuals nitrogen retention remains static or diminishes unless initial values are over about 60 mg per 100 ml of nonprotein nitrogen in the blood (Somogyi zinc precipitate corresponding to 75 to 90 mg per cent by the phosphotungstic acid precipitate method) Time weeks or months In those with higher values azotemia usually but not always progresses to uremia rarely however we have seen relatively acute elevations to 130 to 160 mg per cent return to much lower levels This may occur after 3 weeks or more (Fig 35 36)

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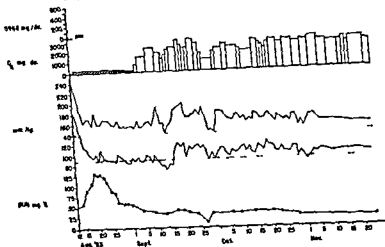


Fig 36 Medication blood pressure and nitrogen retention during hospitalization The solid bars represent oral hydralazine (5968) The cross hatched bars represent parenteral and the open bars oral hexamethonium chloride (C_6) The parenteral dose has been multiplied by 10 in order partially to compensate for the much greater efficacy of this route of administration Each of the points on the blood pressure curve is the average of at least six and initially as many as 24 determinations All were made with the patient supine Note that azotemia is shown in terms of blood urea nitrogen rather than total nonprotein nitrogen

Except for life long enuresis this 18-year-old white male was entirely well until 3 days before he entered the hospital His mother had died with polycystic kidneys Pyrexia and malaise were the initial symptoms followed by lethargy emesis disorientation and coma. Physical examination revealed in addition *papilledema* hemorrhagic retinitis minimal cardiomegaly and a pre systolic gallop Roentgenologic examination suggested *polycystic kidneys* and 3 plus albuminuria was found After returning home the patient did very well He was working when last seen in July 1955 at which time his physical examination including fundoscopic examination was normal His urine contained *no protein* His antihypertensive regimen called for a maximum dose of 750 mg *oral* hexamethonium chloride and a constant dose of 100 mg of hydralazine every *four* hours. His sitting blood pressure at home averaged 160/80 mm. Hg (From Perry H M Jr and Schroeder H A. *Circulation* *14* 105 1956)

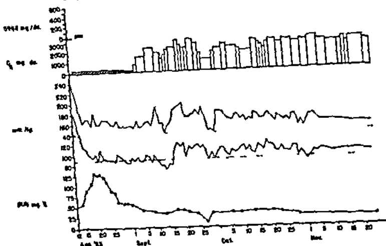


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3 b) The incidence of coronary occlusion appears somewhat lower (after 3 to 5 years) although this disease ac

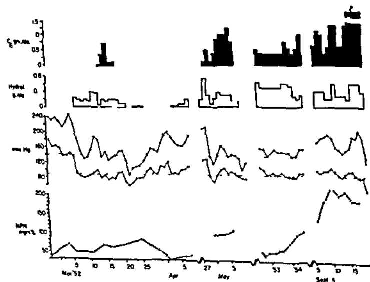


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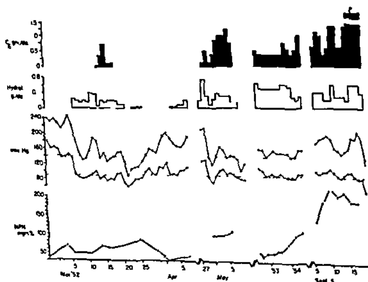


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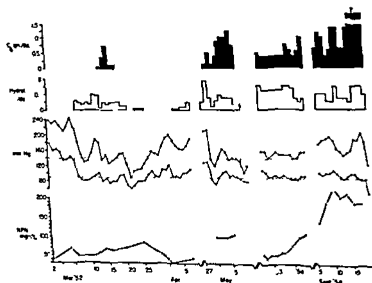


FIG 37 Two directions of progress in azotemia and malignant hypertension. Upper The condition of G B., a 54 year-old man has been static or improving slowly and he has been abl [illegible] full occ [illegible] fair in [illegible] 72 mg [illegible] remain [illegible] static or improved slightly weight and health have increased. Lower That of L. T a 48-year-old man improved at first but azotemia later rapidly progressed to death. Pyelonephritis was found at autopsy the kidneys together weighed 10[illegible] Gm.

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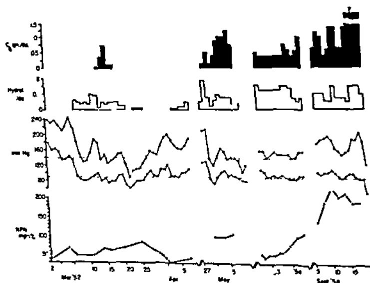


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sponding well to ganglionic blockade alone can be expected to respond to surgery even though the usual lumbodorsal sympathectomy only removes 50 to 60 per cent of the nerves Operation therefore does not become the method of choice when medical measures fail for the opposite holds true i e drugs will work when surgery has failed The one advantage of surgical over chemical sympathectomy is the lack of bother to the patient when the result is successful

According to the data of White (421) when cardiovascular complications occur in hypertensive patients the mortality is high Left ventricular weakness and failure cerebrovascular accidents angina pectoris and myocardial infarctions cause a 3 year mortality rate of 82 per cent and a 10 year mortality rate of 96 per cent with a mean survival time of 4 1 years Surgical sympathectomy alters the 3 year rate to 24 per cent and the 10 year rate to 50 per cent with a mean survival time of 6 1 years for the deceased

TABLE L

MORTALITY RATES AT FOUR YEARS OF PATIENTS SUBJECTED TO SURGICAL SYMPATHECTOMY USUAL MEDICAL MEASURES AND CHEMOTHERAPY (PER CENT)

Smithwick Group	*Smithwick s Series (420) Ae Ages 38–47*		*White s Series (421) Ages 30–60*		*Author s Series Ages 34–76 Chemotherapy*	
	Medical	*Surgical*	*Medical*	*Surgical*	*Stopped*	*Continued*
I	10	3				
II	33	12			—	0
III	58	19	84	24	32	1
IV	87	52			38	3
Azotemia	(100)	†	(100)	†	100	20
					100	45

* Most patients were 40–60

† Not suitable for operation because of high operative mortality

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Chapter IX

A PRELIMINARY APPROACH TO THE TREATMENT OF ATHEROSCLEROSIS

OBVIOUSLY, control of a patient's hypertension will do no more than relieve cardiac strain prevent further nephrosclerosis prevent cerebral hemorrhage and relieve angina pectoris Theoretically it will slow that part of the rate of progression of atherosclerosis which is dependant upon an elevated blood pressure Since atherosclerosis is probably reversible (443) at least in so far as cholesterol-containing plaques are concerned (and possibly calcification (422)) treatment of the whole patient and his diseases becomes essential for prolongation of a life potentially shortened by cardiovascular damage There fore an outline of the method we have used is given here the method involves practical measures based on theoreti cal approaches of most promise Since it is most difficult to measure alterations in this disorder for the better or worse until massive accidents occur only time will tell if the results are favorable

The serial measurement of lipoprotein fractions in blood is a procedure confined to the larger specialized centers Total plasma cholesterol however is readily measured in most hospital laboratories Based upon the assumption that lowered plasma cholesterol will in part prevent deposition of esters in plaques one can attempt to lower these values by using some of the influences discussed in Chapter VII

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in the kind of fat in the American and European diet From 30 to 40 per cent of the caloric intake comes from fat mainly of animal origin The purpose of the diet therefore is to restrict animal fat and hydrogenated vegetable oils and to provide an adequate intake of unsaturated vegetable fats containing linolenic acid The basic rules are

A No obvious fat of animal origin should be eaten Modern methods of fattening cattle for slaughter make a saturated body fat

B No hydrogenated vegetable oils should be used since hydrogenation saturates an unsaturated fatty acid (Table LI)

C Natural fat of vegetable origin containing the higher unsaturated fatty acids can be eaten in amounts as large as practicable since these contain the essential unsaturated fatty acids linolenic and linoleic

D In general reduce the fat content of the diet to about 20 per cent of the caloric intake

The most available sources of essential fatty acids are in soy bean and corn oil with the following iodine numbers

	Iodine No	*Remarks*
Soy bean oil	130	Contains 11% linolenate
Corn oil	115	Contains 0.5% linolenate
Cottonseed oil	105	Contains no linolenate
Sesame oil	103	Contains no linolenate
Peanut oil	85	Atherogenic in animals

In order to obtain enough protein without animal fats the following are recommended

All kinds of fish and shellfish Fish oils have a high iodine number

Poultry and game avoiding the fat (except domestic goose and duck) Chicken fat is high in linoleate

Lean beef lamb and veal Most animal fat is low in

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TABLE LII

CHANGE IN PLASMA CHOLESTEROL WITH ORAL EDTA (1 0 GM /DAY)

Patients	*Sex*	*Age*	*Control* (mg %)	*Change* (mg %)	*Interval* (weeks)	*Major Diagnosis*
W H.	♂	54	293	−154	20	Angina pectoris
B McD	♂	54	278	−150	35	Peripheral vascular disease
J S.	♀	70	276	− 40	4	Arterial hypertension
E. B.	♂	61	253	− 58	16	Coronary occlusion, convalescent
G H	♂	45	252	− 36	25	Angina pectoris
G S.	♀	49	237	− 37	14	Arterial hypertension
E. S.	♂	77	225	− 74	3	Arterial hypertension
E. S.	♂	48	210	+ 18	44	Angina pectoris
H D	♂	63	189	− 49	8	A gina pectoris
R. S.	♂	54	177	− 38	12	Angina pectoris
J B	♀	59	178	+ 16	4	Arterial hypertension
Mea			233	− 55		

vessels and symptoms or signs are present the method of Clarke Clarke and Mosher for removing metastatic calcium may be used (422) Trisodium EDTA, 5 0 Gm in 500 ml 5 per cent glucose solution is slowly infused intravenously over 2 to 6 hours The patient is taught to slow the infusion at the appearance of unusual symptoms Strangely enough hypocalcemic tetany does not appear under these precautions Ionized calcium salts and calcium chelated to proteins and peptides at a weaker stability constant than 10 6 (Log K_2 EDTA) are probably removed the strongly chelated calcium in bone is probably not

An injection is given daily for 5 days 2 days are allowed for rest and the 5-day course repeated After a month or more for evaluation of symptoms a second 50 Gm is administered

RESULTS EXPECTED

In Table LII are shown changes in blood cholesterol levels using calcium disodium ethylenediamine tetra acetate (Calcium Versenate) in doses of 1 0 Gm per day In Table LIII are shown the changes produced by this agent

TABLE LII

CHANGE IN PLASMA CHOLESTEROL WITH ORAL EDTA (1 0 GM /DAY)

Patients	*Sex*	*Age*	*Control* (mg %)	*Change* (mg %)	*Interval* (weeks)	*Major Diagnosis*
W H.	♂	54	293	−154	20	Angina pectoris
B McD	♂	54	278	−150	35	Peripheral vascular disease
I S.	♀	70	276	− 40	4	Arterial hypertension
E. B.	♂	62	253	− 58	16	Coronary occlusion, convalescent
G H	♂	45	252	− 36	25	Angina pectoris
G S.	♀	49	237	− 37	14	Arterial hypertension
E. S.	♂	77	225	− 74	3	Arterial hypertension
E. S.	♂	48	210	+ 18	44	Angina pectoris
H D	♂	63	189	− 49	8	A gina pectoris
R. S.	♂	54	177	− 38	12	Angina pectoris
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with diet and vitamin B_6 added In general the cholesterol changes are downward although in some cases they are resistant to all three forms of therapy Some depressed values did not rise when EDTA was discontinued an expected result if trace metals were being removed

All patients with angina pectoris were relieved of attacks of pain either completely or partly in that they occurred less than once a month No electrocardiographic changes in the direction of normal were observed No signs of hepatocellular damage developed

Comment While untried for periods long enough to evaluate these results on the disease there is little doubt that cholesterol values can become quite low by this form of treatment Changes in the degree of atherosclerosis are difficult to measure but rough estimates of improvement in the disease can be estimated especially when it has advanced far enough to give local ischemic symptoms In the coronary arteries relief of angina pectoris if it is real and not imaginary suggests resorption of plaques In the aorta lessening of the widened pulse pressure suggests a return of aortic elasticity In the legs relief of claudication indicates improvement in blood flow In the cerebral area abolition of minor paraesthesias and paralytic episodes indicates reabsorption of plaques Some changes may be expected in time except for a return of aortic elasticity

Therefore if degenerative cardiovascular disease is to be treated as m ny prod
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manifestations include emotional tension anxiety, excessive drive nervousness and the diencephalic blush The blush is induced by histamine and resembles that seen with excessive quantities of circulating serotonin tension nervousness anxiety result in some individuals from epinephrine isoamylamine tyramine and those synthetic or natural methylated analogues which inhibit cerebral monamine oxidase (ephedrine amphetamine etc.) thus preventing oxidative deamination of naturally occurring substances

From the huge amounts of tranquillizers sold the American public one might believe that chemically mediated nervous disorders were almost a national disorder That many individuals might be so affected could be inferred from the abnormal trace metal content of American tissues if one interfered with vanadium or monamine oxidase or there was deficiency of vanadium primary amines could be implicated as causes of a widespread cerebral disorder

Hereditary The ability to react to stress by vasospasm is an hereditary trait apparently transmitted as a Mendelian dominant

Neurogenic The sympathetic nervous system is over active most likely because of increased cortico-hypothalamic activity The posterior hypothalamus for which serotonin has a predilection is apparently stimulated more than is the anterior the chemical mediator of which is not known Cortico-hypothalamic activity is increased as a result of somatically formed primary amines Neurogenic vasospasm causes neurogenic renal ischemia

Renal Renal disturbances dependent upon ischemia produce humoral vasoconstrictor substances Trace metals both normal and abnormal are involved Two metabolic pathways may be considered

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B Renin is released possibly because of the acidity secondary to the lessened formation of ammonia (renin is extracted from kidney only at acid pH) This postulate is unproven and not too sound but we have no better one Renin comes from the superficial areas of the cortex of the kidney which becomes markedly acid when the renal artery is constricted Adjustments take place with time—several weeks

Result

a) Hypertensin (angiotonin) is formed in blood at first through the physical release of renin (found)

b) With time renin itself is no longer released into blood but continues to act *in situ* (not proven but renin disappears from blood) Perhaps renin is slowly modified into a somewhat different proteolytic enzyme

c) Hypertensin I or its analogue formed in kidney inactive on blood vessels becomes activated either 1) through decarboxylation leaving an active terminal NH_2 the decarboxylase being in blood and kidney or 2) through action of a specific peptidase splitting off one or two amino acids and leaving a terminal $-NH_2$ In this latter event the peptidase would necessarily be a manganous enzyme The second pathway is the more logical one as peptidases are known and peptide decarboxylases are not Ordinarily in the absence of renal ischemia the small amounts of renin released into the renal venous blood form hypertensin which is inactivated both in kidney and in blood In renal ischemia the shift of locus of catabolism of hypertensin is from kidney to peripheral vasculature (theoretical but monamine oxidase acts on both hypertensin and pherentasin both peptides and it probably occurs in smooth muscle of blood vessels)

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The net results would be cortical acidity less urinary ammonia and sodium wastage, the same as those found in organic renal ischemia but appearing by somewhat different routes Primary amines in blood however would not be elevated (Fig 38)

(If cortical acidity is the stimulus for the action of renin hypertensin I would be formed *in situ* and released into renal venous blood where it would be converted to hypertensin II (pherentasin) by action of a specific manganous peptidase Thus both organic renal ischemia and cadmium can cause the same end results Naturally renal ischemia accompanying neurogenic or pherentasin vasoconstriction would call into action pathway I

Therefore trace metals can be involved in the hypothetical peptidase probably manganous which converts hypertensin I to hypertensin II, in monamine oxidase which inactivates it, in the decarboxylases and amine oxidases which are concerned in the hypertensive state and even in tyrosinase (copper) which can inactivate norepinephrine epinephrine hydroxytyramine and tyramine)

Therapeutic Note Drugs or procedures which block sympathetic nerve impulses will counteract only the neurogenic portion of hypertension Drugs or procedures which a) act to dilate vascular smooth muscle b) increase renal plasma flow, or c) inactivate hypertensin II or pherentasin, will counteract the nephrogenic portion of hypertension All known inactivators are metal binding or chelating agents

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The actions of hydralazine are fourfold

1 Decarboxylase inhibition with the result that renal amino acid metabolism is further suppressed and therefore less primary amine is formed

2 Monamine oxidase stimulation with the result that those primary amines which are formed are oxidized more readily These include pherentasin or hypertensin II

3 Hypertensin and pherentasin are both directly in activated either through carbonyl linkage or what is more probable removal of a chelated trace metal necessary for the integrity of the peptides

4 *Constricted* vascular smooth muscle is dilated no matter what causes the constriction by some unknown process which could be dependent either upon carbonyl or sulfhydryl binding or upon metal chelation

In addition histaminase is inhibited a reaction common to many hydrazides

Adrenocortical Renal sodium wastage (or need as in heart failure) probably causes adrenal cortical production of aldosterone (theoretical but logical) This steroid probably sensitizes blood vessels to circulating vasoactive amines and sympathetic discharges through intracellular sodium potassium alterations (proven only for DOCA) Most cases of hypertension exhibit secondary aldosteronism because of renal sodium wastage

Primary aldosteronism by sensitizing vascular smooth muscle to normally circulating vasoactive amines and normal sympathetic tone can produce a moderate degree of hypertension with normal renal plasma flow Cases of this nature are not unusual This type of hypertension while benign can slowly develop into a more serious variety with congestive heart failure the usual end result

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(2) Cholesterol has a predilection for making unsaturated fatty acid esters When insufficient unsaturated fatty acids are available for esterification saturated fatty acids are used These esters are quite insoluble and probably have lower specific gravities Possibly breakdown metabolism or excretion of cholesterol is more easily accomplished when esters are unsaturated than when made of saturated long chain fatty acids

These two ideas are highly speculative The mechanism of lowering plasma cholesterol by essential fatty acids is not understood

Factors which may influence the deposition of cholesterol esters in sub-intimal spaces are

C *Physical*—Intra arterial pressure and changes of pressure (turbulence) at bifurcations of major vessels (Found)

D *Metabolic*—Pyridoxal deficiency causes sub-intimal lesions identical microscopically to pre atherosclerotic lesions observed in animals and man (Found)

a) Pyridoxal is necessary for the integrity of the mucopolysaccharides of sub-intimal ground substance (Inferred)

b) Pyridoxal affects fatty acid metabolism by promoting the synthesis of essential fatty acids from less unsaturated ones (Found)

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application of therapy present and to come Rapid im provements are expected

(1) Reduce blood pressure of hypertensive patients to a mean level of 140/90 mm Hg (or as low as tolerable) and keep it there indefinitely Two drugs are usually necessary given frequently regularly and carefully one should act on nerves and the other on vascular smooth muscle

(2) Lower plasma cholesterol to 120 to 160 mg per 100 ml (or about the same levels in mg per cent as systolic pressure is in mm Hg!) This can be accomplished slowly in some individuals and soon will be in most by

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It is a long step from a lowered cholesterol to absorp tion of plaques but the assumption is reasonable

There are enough ideas now under experimental ob servation to strengthen the belief that atherosclerosis is a reversible disease at least in so far as the fatty and calcific deposits are concerned Arterial hypertension in man can be controlled indefinitely and sometimes reversed Ap plication of therapy to both diseases in the same individual may be expected to reverse in part the lethal and disabling effects of each

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1b SCHROEDER H. A.. Generalized vasospasm and arterial hypertension in *Signs and Symptoms* 3rd Ed. edited by C. M MacBryde Philadelphia Lippincott 1957

1c. SCHROEDER, H. A.. Arterial hypertension. Veteran s Administration Technical Bulletin TB 10-59 November 1949

2 MORITZ A R., AND OLDT M R.. Arteriolar sclerosis in hypertensive and nonhypertensive individuals *Am J Path 13*6 9 1937

3 SCHROEDER, H A AND DAVIES D F Studies on essential hypertension V An endocrine hypertensive syndrome. *Ann Int Med 40* 516 1954

3b SCHROEDER, H A., DAVIES, D F AND CLARK H E. A syndrome of hypertension obesity menstrual irregularities and evidence of adrenal cortical hyperfunction. *J Lab & Clin Med 34* 1746 1949

3c. DAVIES D F AND CLARK, H E. A hypertensive syndrome with relative adrenal cortical overactivity *Circulation* 2 481 1950

4 SCHROEDER, H A *Hypertensive Diseases—Causes and Control* Philadelphia Lea & Febiger 1953

5 PERRY H M JR., O NEAL, R. M., AND THOMAS W A.. Pulmonary disease following chronic chemical ganglionic blockade A clinical and pathologic study *Am. J Med 22* 37 19 7

6 GOLDBLATT H *The Renal Origin of Hypertension* Springfield Thomas 1948

7 DAMMIN G J GOLDMAN M L., SCHROEDER, H A., AND PACE M G Arterial hypertension in dogs II The effects of neurogenic hypertension with a study of periodic renal biopsies over a seven year period *Lab Investigation 5* 72 1956

7b GOLDMAN M L., SCHROEDER, H. A. AND DAMMIN G J Renal changes in experimental hypertension. *Am J Med 14* 751 1953

7c. DAMMIN G J., GOLDMAN M L., SCHROEDER H A., AND PACE M G The effects of prolonged experimental hypertension in the dog with a study of periodic renal biopsies over a seven year period *Am J Path 31* 587 1955

8 SNAPPER, I *Chinese Lessons to Western Medicine* New York, Interscience 1941

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Schroeder H A.. Personality factors in arterial hypertension *J.A.M.A* 140:265 1949

27 Binger, C. A Ackerman N W., Cohn A. E., Schroeder, H A., and Steele, J M.. *Personality in Arterial Hypertension* (Psychosomatic Medicine Monographs) New York, Robert Brunner 1945

28 Pickering G W.. The genetic factor in essential hypertension *Ann Int Med* 43:457 1955

29 Schroeder H A "Essential" hypertension A concept of its Mechanism *Am J M Sc* 204:734 1942

30 Schroeder H A.. The pathogenesis of hypertension *Am J Med* 10:189 1951

31 Schroeder H A., and Steele J M Studies on "essential" hypertension I. Classification *Arch Int Med* 64:927 1939

32 Bays, R. P., and Scrimshaw N S Facts and fallacies regarding the blood pressure of different regional and racial groups. *Circulation* 8:655 1953

33 Williams, A. W.. Heart disease in the native population of Uganda. Part IV Hypertensive heart disease *East African M J.*, 21:328 1944

34 Cohen B M Arterial hypertension among Indians of the south western United States *Am J M Sc.*, 225:505 1953

35 Williams A. W Ball, J D and Davies J N P Endomyocardial fibrosis in Africa Its diagnosis distribution and nature *Tr Roy Soc. Trop Med & Hyg* 48:290, 1954

36 Janeway T C. The Clinical Study of Blood Pressure New York Appleton 1904

37 Schroeder, H A., and Menhard E. M Spontaneous variations of blood pressure in hypertensive and normotensive individuals *Am Heart J.*, 51:577 1956

38 Raab W *Hormonal and Neurogenic Cardiovascular Disorders* Balt —

39 Gubner

pres-

40 Smithwick, R. H., and Robertson C. W The phenomenon of hyperactivity Definition *Angiology* 2:148 1951

41 Reiser, M., and Ferris E. B Jr. The nature of the cold pressor test and its significance in relation to neurogenic and humoral mechanisms in hypertension *J Clin Investigation*, 27:156 1948

42. Hess W R. *Die Regulierung des Blutkreislaufs* Leipzig G Thieme 1930

43 Heymans C., Nowak J G., and Samaan A Sur l'action vasomotrice réflexe centrale et périphérique del l'acide carbonique de l'anoxemie et de l'asphyxie *Compt rend Soc biol Paris* 11:248 1934.

SCHROEDER H A.. Personality factors in arterial hypertension *JAMA* 140:265 1949
27 BINGER, C. A ACKERMAN N W., COHN A. E., SCHROEDER, H A., AND STEELE, J M.. *Personality in Arterial Hypertension* (Psychosomatic Medicine Monographs) New York, Robert Brunner 1945
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31 SCHROEDER H A., AND STEELE J M Studies on "essential" hypertension I. Classification *Arch Int Med* 64 927 1939
32 BAYS, R. P., AND SCRIMSHAW N S Facts and fallacies regarding the blood pressure of different regional and racial groups. *Circulation* 8 655 1953
33 WILLIAMS, A. W.. Heart disease in the native population of Uganda. Part IV Hypertensive heart disease *East African M J.*, 21 328 1944
34 COHEN B M Arterial hypertension among Indians of the south western United States *Am J M Sc.*, 225 505 1953
35 WILLIAMS A. W BALL, J D AND DAVIES J N P Endomyocardial fibrosis in Africa Its diagnosis distribution and nature *Tr Roy Soc. Trop Med & Hyg* 48 290, 1954
36 JANEWAY T C. *The Clinical Study of Blood Pressure* New York Appleton 1904
37 SCHROEDER, H A., AND MENHARD E. M Spontaneous variations of blood pressure in hypertensive and normotensive individuals *Am Heart J.*, 51.577 1956
38 RAAB W *Hormonal and Neurogenic Cardiovascular Disorders* Balt —
39 GUBNER
pres-
40 SMITHWICK, R. H., AND ROBERTSON C. W The phenomenon of hyperactivity Definition *Angiology* 7 14? 1951
41 REISER, M., AND FERRIS E. B JR. The nature of the cold pressor test and its significance in relation to neurogenic and humoral mechanisms in hypertension *J Clin Investigation*, 27 156 1948
42. HESS W R. *Die Regulierung des Blutkreislaufs* Leipzig G Thieme 1930
43 HEYMANS C., NOWAK J G., AND SAMAAN A Sur l'action vasomotrice réflexe centrale et périphérique de l'acide carbonique de l'anoxémie et de l'asphyxie *Compt rend Soc biol Paris* 11 248 1934.

and gastric motility of stimulation of orbital surface of frontal lobe *J Neurophysiol.*, 3 276 1940

56c. Pool, J. L. The visceral brain of man. *J Neurosurg.*, 11 45 1954

57 Mann P J G and Quastel, J H. Benzedrine (β phenylisopropyl amine) and brain metabolism. *Biochem J.*, 34 414 1940

58 Fellows E. J., and Bernheim F The effect of a number of aral kylamines on the oxidation of tyramine by amine oxidase. *J Pharmacol & Exper Therap* 100 94 1950

59 Toman J E. P., and Davis J P The effects of drugs upon the electrical activity of the brain *Pharmacol Rev.*, 1 425 1949

60 Brodie, B B., Pletscher A., and Shore, P A Evidence that serotonin has a role in brain function Science 12? 968 195

60b. Udenfriend S., Weissbach H., and Bogdanski D F. Biochemical findings relating to serotonin action. *Ann New York Acad Sc.*, 66 Art 3 1956

61 Sjoerdsma A Weissbach H and Udenfriend S A clinical physiologic and biochemical study of patients with malignant car cinoid (argentaffinoma) *Am J Med.*, 20 5?0 1956

62 Schroeder H A., and Goldman M L. A test for the presence of the 'hypertensive diencephalic syndrome' using histamine. *Am J Med* 6 16? 1949

63 Page, I H Serotonin (5-hydroxytryptamine) *Physiol Rev.*, 34 563 1954

64 Bordley J III. and Baker, B M Jr. A consideration of arterio sclerosis of the cerebral vessels and the pathogenesis of hyperten sion *Bull Johns Hopkins Hosp* 39 229 1926

65 Pletscher, A Shore, P A and Brodie, B B Serotonin release as a possible mechanism of reserpine action. Science 122 374 1955

65b Shore, P A. Role of brain serotonin in reserpine action. *Ann New York Acad Sc* 66 Art. 3 1956

66 Shore, P A Silver, S L., and Brodie B B. Interaction of reser pine serotonin and lysergic acid diethylamide in brain *Science* 122 284 1955

67 Selling L. S and Selling P H Clinical study of a new tran quilizing drug *J.A.M.A* 157 1594 1955

68 Weiskrantz L., and Wilson W A., Jr. The effects of reserpine on emotional behavior of normal and brain-operated monkeys *Ann New York Acad Sc.*, 61 86 1955

69 Schroeder, H A Hypertensive vascular disease Therapy with modern drugs and its limits *J Chronic Dis* 1 497 1955

70 Schroeder, H A., and Perry H M Jr. Psychosis apparently produced by reserpine. *J.A.M.A* 159 839 1955

70b Muller, J C. Pryor, W W., Gibbons J E., and Orgain E. S

and gastric motility of stimulation of orbital surface of frontal lobe *J Neurophysiol.*, 3 276 1940

56c. Pool, J. L. The visceral brain of man. *J Neurosurg.*, 11 45 1954

57 Mann P J G and Quastel, J H.. Benzedrine (β phenylisopropyl amine) and brain metabolism. *Biochem J.*, 34 414 1940

58 Fellows E. J., and Bernheim F The effect of a number of aral kylamines on the oxidation of tyramine by amine oxidase. *J Pharmacol & Exper Therap* 100 94 1950

59 Toman J E. P., and Davis J P The effects of drugs upon the electrical activity of the brain *Pharmacol Rev.*, 1 425 1949

60 Brodie, B B., Pletscher A., and Shore, P A Evidence that serotonin has a role in brain function Science 122 968 195

60b. Udenfriend S., Weissbach H., and Bogdanski D F.. Biochemical findings relating to serotonin action. *Ann New York Acad Sc.*, 66 Art 3 1956

61 Sjoerdsma A Weissbach H and Udenfriend S A clinical physiologic and biochemical study of patients with malignant car cinoid (argentaffinoma) *Am J Med.*, 20 520 1956

62 Schroeder H A., and Goldman M L.. A test for the presence of the 'hypertensive diencephalic syndrome' using histamine. *Am J Med* 6 162 1949

63 Page, I H Serotonin (5-hydroxytryptamine) *Physiol Rev.*, 34 563 1954

64 Bordley J III. and Baker, B M Jr. A consideration of arteriosclerosis of the cerebral vessels and the pathogenesis of hypertension *Bull Johns Hopkins Hosp* 39 229 1926

65 Pletscher, A Shore, P A and Brodie, B B Serotonin release as a possible mechanism of reserpine action. Science 122 374 1955

65b Shore, P A. Role of brain serotonin in reserpine action. *Ann New York Acad Sc* 66 Art. 3 1956

66 Shore, P A Silver, S L., and Brodie B B.. Interaction of reserpine serotonin and lysergic acid diethylamide in brain *Science* 122 284 1955

67 Selling L. S and Selling P H Clinical study of a new tranquilizing drug *J.A.M.A* 157 1594 1955

68 Weiskrantz L., and Wilson W A., Jr. The effects of reserpine on emotional behavior of normal and brain-operated monkeys *Ann New York Acad Sc., 61* 36 1955

69 Schroeder, H A Hypertensive vascular disease Therapy with modern drugs and its limits *J Chronic Dis* 1 497 1955

70 Schroeder, H A., and Perry H M Jr. Psychosis apparently produced by reserpine. *J.A.M.A* 159 839 1955

70b Muller, J C. Pryor, W W., Gibbons J E., and Orgain E. S

81 McCubbin J W., Green J H., and Page, I H.. Baroceptor function in chronic renal hypertension Circulation Res., 4 205 1956
82. Ogden E The relation of the nervous system to acute and chronic experimental hypertension in *Factors Regulating Blood Pressure* Transactions of the First Conference ed by Zweifach B W., and Shorr E., New York Macy 1947 p 12.
83 Zawoiski E. J Baer J E., Braunschweig L. W., Paulson S F., and Shermer, A.. Gastrointestinal secretion and absorption of 3 methyl aminoisocamphane hydrochloride (mecamylamine) *Federation Proc* 15 205 1956
84 Goodman L. S and Gilman A. *The Pharmacological Basis of Therapeutics* 2nd Ed New York, Macmillan, 1955
85 Furchgott R. F., and Bhadrakom S Reactions of strips of rabbit aorta to epinephrine isopropylarterenol sodium nitrate and other drugs *J Pharmacol & Exper Therap* 108 129 1953
85b Furchgott R. F The pharmacology of vascular smooth muscle *Pharmacol Rev* 7 183 1955
86 Bing R. J and Zucker, M B Renal hypertension produced by amino acid. *J Exper Med.*, 74 235 1941
87 Holtz P Credner K and Walter, H Uber die Spezifitat der Aminosauredecarboxlasen. *Ztschr physiol Chem.*, 262 111 1939
88. Blaschko H., Richter, D., and Schlossmann H The oxidation of adrenalin and other amines *Biochem J* 31 2187 1937
89 Kohn H I Tyramine oxidase *Biochem J* 31 1693 1937
90 Stock C. C., and Schroeder, H A.. Pressor substances in arterial hypertension Activity and amine content of crude extracts of blood. *Am J Physiol* 160 409 1950
91 Schroeder H A and Olsen N S Pressor substances in arterial hypertension II. Demonstration of pherentasin a vasoactive material procured from blood *J Exper Med* 92 545 1950
92. Council on Pharmacy and Chemistry Blood dycrasias associated with chlorpromazine therapy *J.A.M.A* 160 287 1956
93 Morrow J D., Schroeder, H A., and Perry H M., Jr. Studies on the control of hypertension by Hyphex. II. Toxic reactions and side effects *Circulation* 8 829 1953
94. Morrison B Parenteral hexamethonium in hypertension. *Brit M J* 1 1291 19 3
95 Balst A. A. and Ferris F B Varying patterns of blood pressure response to autonomic blockade Implications concerning the interplay of neurogenic and humoral factors in control of vascular tone. Proc. Annual Meeting Council For High Blood Pressure Research, Am Heart A., Nov 1955
96 Olsen N S., and Schroeder, H. A.. Oxygen tension and pH of the

81 McCubbin J W., Green J H., and Page, I H.. Baroceptor function in chronic renal hypertension Circulation Res., 4 205 1956
82. Ogden E The relation of the nervous system to acute and chronic experimental hypertension in *Factors Regulating Blood Pressure* Transactions of the First Conference ed by Zweifach B W., and Shorr E., New York Macy 1947 p 12.
83 Zawoiski E. J Baer J E., Bruanschweig L. W., Paulson S F., and Shermer, A.. Gastrointestinal secretion and absorption of 3 methyl aminoisocamphane hydrochloride (mecamylamine) *Federation Proc* 15 205 1956
84 Goodman L. S and Gilman A. *The Pharmacological Basis of Therapeutics* 2nd Ed New York, Macmillan, 1955
85 Furchgott R. F., and Bhadrakom S Reactions of strips of rabbit aorta to epinephrine isopropylarterenol sodium nitrate and other drugs *J Pharmacol & Exper Therap* 108 129 1953
85b Furchgott R. F The pharmacology of vascular smooth muscle *Pharmacol Rev* 7 183 1955
86 Bing R. J and Zucker, M B Renal hypertension produced by amino acid. *J Exper Med.*, 74 235 1941
87 Holtz P Credner K and Walter, H Uber die Spezifitat der Aminosauredecarboxlasen. *Ztschr physiol Chem.*, 262 111 1939
88. Blaschko H., Richter, D., and Schlossmann H The oxidation of adrenalin and other amines *Biochem J* 31 2187 1937
89 Kohn H I Tyramine oxidase *Biochem J* 31 1693 1937
90 Stock C. C., and Schroeder, H A.. Pressor substances in arterial hypertension Activity and amine content of crude extracts of blood. *Am J Physiol* 160 409 1950
91 Schroeder H A and Olsen N S Pressor substances in arterial hypertension II. Demonstration of pherentasin a vasoactive material procured from blood *J Exper Med* 92 545 1950
92. Council on Pharmacy and Chemistry Blood dycrasias associated with chlorpromazine therapy *J.A.M.A* 160 287 1956
93 Morrow J D., Schroeder, H A., and Perry H M., Jr. Studies on the control of hypertension by Hyphex. II. Toxic reactions and side effects *Circulation* 8 829 1953
94. Morrison B Parenteral hexamethonium in hypertension. *Brit M J* 1 1291 1953
95 Balst A. A. and Ferris F B Varying patterns of blood pressure response to autonomic blockade Implications concerning the interplay of neurogenic and humoral factors in control of vascular tone. Proc. Annual Meeting Council For High Blood Pressure Research, Am Heart A., Nov 1955
96 Olsen N S., and Schroeder, H. A.. Oxygen tension and pH of the

109b Ek J The influence of heavy hydration on the renal function in normal and hypertensive man *Scandinav J Clin & Lab Invest.*, 7 Suppl 19 pp 1 77 1955

109c. Friedman S M., Hardwick D F and Hinke, J A M.. The effect of pitressin on sodium tolerance in experimental hypertension *Circulation Res* 3 490 1955

109d Friedman S M Hinke J A M., and Hardwick D F Sodium tolerance in experimental hypertension *Circulation Res* 3 297 1955

110 Farnsworth E. B Renal reabsorption of chloride and phosphate in normal subjects and in patients with essential arterial hyper tension *J Clin Investigation* 25 897 1946

110b. Green D M., Johnson A. D., Bridges W C. and Lehmann J H Stages of salt exchange in essential hypertension *Circulation* 9 416 1954

110c. Cottier P T Hoobler S W and Weller J M.. Effects of a sodium chloride load on renal hemodynamics and electrolyte excretion in essential hypertension *J Clin Investigation* 35 698 1956

111 Perry H M Jr and Schroeder, H A Personal observations from our laboratories

112 Schroeder, H A and Olsen N S Humoral pressor substances and their relation to arterial hypertension Am Chemical Soc. "Advances in Chemistry Series No 2 Chemical Factors in Hyper tension May 23 1950

112b Goldman M L Kriss J P Futcher, P H and Schroeder H A The transfusion of arterial hypertensive and normotensive blood into hypertensive subjects *Am J M Sc 21, 651* 1949

112c. Olsen N S Schroeder, H A and Menhard E M *Effect of certain amines on the blood pressure of normotensive and hyperten sive rats* Proc Soc Exper Biol & Med 74 581 1950

113 Grollman A The Pathogenesis of Experimental and Clinical Hyper tensive Cardiovascular Disease *Proc Council For High Blood Pressure Research* Am Heart A. New York 1955

114 Edinger, E. F Jr. and Olsen N S Urine amine levels in normo tensive and hypertensive subjects *Federation Proc* 9 36 1950

115 Davies D F Wolfe, K. M and Perry H M Jr *Studies* on primary amines II Their natural *occurrence* in urine of normotensive and hypertensive subjects *J Lab & Clin* Med 43 620 1954

116 Croxatto H and Croxatto R.. Inhibitory *action* of amineoxidase and tyrosinase upon vasoconstrictor *effect* of hypertensin. *Proc Soc Exper Biol & Med* 48 892 1941

117 Schroeder, H A.. *The* effect of a preparation of amine oxidase on experimental hypertension *Science* 95 306 1942.

118 Relei F C. and Futcher, P H The effects of histamine on renal

109b Ek J The influence of heavy hydration on the renal function in normal and hypertensive man Scandinav J Clin & Lab Invest., 7 Suppl 19 pp 1 77 1955
109c. Friedman S M., Hardwick D F and Hinke, J A M.. The effect of pitressin on sodium tolerance in experimental hypertension Circulation Res 3 490 1955
109d Friedman S M Hinke J A M., and Hardwick D F Sodium tolerance in experimental hypertension Circulation Res 3 297 1955
110 Farnsworth E. B Renal reabsorption of chloride and phosphate in normal subjects and in patients with essential arterial hypertension J Clin Investigation 25 897 1946
110b. Green D M., Johnson A. D., Bridges W C. and Lehmann J H Stages of salt exchange in essential hypertension Circulation 9 416 1954
110c. Cottier P T Hoobler S W and Weller J M.. Effects of a sodium chloride load on renal hemodynamics and electrolyte excretion in essential hypertension J Clin Investigation 35 698 1956
111 Perry H M Jr and Schroeder, H A Personal observations from our laboratories
112 Schroeder, H A and Olsen N S Humoral pressor substances and their relation to arterial hypertension Am Chemical Soc. "Advances in Chemistry Series No 2 Chemical Factors in Hypertension May 23 1950
112b Goldman M L Kriss J P Futcher, P H and Schroeder H A The transfusion of arterial hypertensive and normotensive blood into hypertensive subjects Am J M Sc 21, 651 1949
112c. Olsen N S Schroeder, H A and Menhard E M Effect of certain amines on the blood pressure of normotensive and hypertensive rats Proc Soc Exper Biol & Med 74 581 1950
113 Grollman A The Pathogenesis of Experimental and Clinical Hypertensive Cardiovascular Disease Proc Council For High Blood Pressure Research Am Heart A. New York 1955
114 Edinger, E. F Jr. and Olsen N S Urine amine levels in normotensive and hypertensive subjects Federation Proc 9 36 1950
115 Davies D F Wolfe, K. M and Perry H M Jr Studies on primary amines II Their natural occurrence in urine of normotensive and hypertensive subjects J Lab & Clin Med 43 620 1954
116 Croxatto H and Croxatto R.. Inhibitory action of amineoxidase and tyrosinase upon vasoconstrictor effect of hypertensin. Proc Soc Exper Biol & Med 48 592 1941
117 Schroeder, H A.. The effect of a preparation of amine oxidase on experimental hypertension Science 95 306 1942.
118 Reley F C. and Futcher, P H The effects of histamine on renal

acute glomerulonephritis *Proc Soc Exper Biol & Med* 33 288 1934

131 Merrill A J Morrison J L., and Brannon E. S Concentration of renin in renal venous blood in patients with chronic heart failure. *Am J Med* 1 468 1946.

132. Shipley R E., Helmer O M and Kohlstaedt K G.. The presence in blood of a principle which elicits a sustained pressor response in nephrectomized animals *Am J Physiol* 149 708 1947

133 Davies D F., Wolfe K. M., and Perry H M., Jr. Studies on primary amines I Methods. *J Lab & Clin Med* 41 802 1953

134 Davies D F Wolfe, K. M., Perry H M., Jr., Schroeder H A., and Menhard E. M Chemical characteristics of pressor amines extracted from urine. *Federation Proc.* 12 467 1953

134b Davies D F Miller, H and Schroeder H A.. Association between primary amines and pressor substances in urine *Am J Med* 11 240 1951

135 Perry H M Jr and Goldstein G Studies on primary amines III. Limiting and optimum conditions for quantitative determination by the ninhydrin method *J Lab & Clin Med* 45 963 1955

136 Wakerlin G E and Johnson C. A Reductions in blood pressures of renal hypertensive dogs by hog renin Proc *Soc Exper Biol & Med* 46 104 1941

137 Frank M H Graham L., and Wakerlin G E. Treatment and prophylaxis of experimental hypertension in monkeys with renins and antirenins Federation Proc 15 66 1956

138 Skeggs L. T Jr., Marsh W H., Kahn J R., and Shumway N P.. The existence of two forms of hypertensin. *J Exper Med* 99 275 1954

138b Helmer, O M Use of rabbit aortic strips to biologically differenti [illegible]

138c. B [illegible]

tion Proc 15 226 1956

139 Skeggs L. T., Jr Marsh W H Kahn J R. and Shumway N P Amino acid composition and electrophoretic properties of hypertensin I. *J Exper Med* 102 435 1955

140 Smith E. L Aspects of the Specificity and Mode of Action of Some Peptidases in *Enzymes and Enzyme Systems* Edsall J T., ed Cambridge Harvard 19[illegible]

141 Skeggs, L T Jr., Kahn J R. and Shumway N P The purification of hypertensin II *J Exper Med.,* 103 301 1956

141b. Skeggs L. T *Jr. Kahn J R.,* and Shumway N P.. The preparation and function of the hypertensin-converting enzyme *J Exper Med* 103 295 1956

acute glomerulonephritis *Proc Soc Exper Biol & Med* 55 288 1944

131 MERRILL A J MORRISON J L., AND BRANNON E. S Concentration of renin in renal venous blood in patients with chronic heart failure. *Am J Med* 1 468 1946.

132. SHIPLEY R E., HELMER O M AND KOHLSTAEDT K G.. The presence in blood of a principle which elicits a sustained pressor response in nephrectomized animals *Am J Physiol* 149 708 1947

133 DAVIES D F., WOLFE K. M., AND PERRY H M., JR. Studies on primary amines I Methods. *J Lab & Clin Med* 41 802 1953

134 DAVIES D F WOLFE, K. M., PERRY H M., JR., SCHROEDER H A., AND MENHARD E. M Chemical characteristics of pressor amines extracted from urine. *Federation Proc.* 12 467 1953

134b DAVIES D F MILLER, H AND SCHROEDER H A.. Association between primary amines and pressor substances in urine *Am J Med* 11 240 1951

135 PERRY H M JR AND GOLDSTEIN G Studies on primary amines III. Limiting and optimum conditions for quantitative determination by the ninhydrin method *J Lab & Clin Med* 45 963 1955

136 WAKERLIN G E AND JOHNSON C. A Reductions in blood pressures of renal hypertensive dogs by hog renin *Proc Soc Exper Biol & Med* 46 104 1941

137 FRANK M H GRAHAM L., AND WAKERLIN G E. Treatment and prophylaxis of experimental hypertension in monkeys with renins and antirenins Federation Proc 15 66 1956

138 SKEGGS L. T JR., MARSH W H., KAHN J R., AND SHUMWAY N P.. The existence of two forms of hypertensin. *J Exper Med* 99 275 1954

138b HELMER, O M Use of rabbit aortic strips to biologically differenti

138c. B [illegible]

tion *Proc* 15 226 1956

139 SKEGGS L. T., JR MARSH W H KAHN J R. AND SHUMWAY N P Amino acid composition and electrophoretic properties of hypertensin I. *J Exper Med* 102 435 1955

140 SMITH E. L Aspects of the Specificity and Mode of Action of Some Peptidases in *Enzymes and Enzyme Systems* Edsall J T., ed Cambridge Harvard 1951

141 SKEGGS, L T JR., KAHN J R. AND SHUMWAY N P The purification of hypertensin II *J Exper Med.*, 103 301 1956

141b. SKEGGS L. T JR. KAHN J R., AND SHUMWAY N P.. The preparation and function of the hypertensin-converting enzyme *J Exper Med* 103 295 1956

158 YULE, C. L. Obstructive lesions of the main renal artery in relation to hypertension. *Am J M Sc* 07:394 1944

159 CASTLEMAN B and SMITHWICK R. H The relation of vascular disease to the hypertensive state *New England J Med* 239:732, 1948

160 WILSON C. AND BYROM F B Renal changes in malignant hypertension. *Lancet* 1 136 1939

161 SCHROEDER H A Arterial hypertension in rats I. Methods *J Exper Med* 75:513 1942

16_ SCHROEDER H A., AND NEUMANN C., Arterial hypertension in rats. II. Effects on the kidneys. *J Exper Med* 75 527 1942

163 SPITZNAGEL, J K., AND SCHROEDER, H A Experimental pyelonephritis and hypertension in rats *Proc Soc Exper Biol & Med.*, 77:762 1951

164 FLASHER J AND DRURY D F Effects of removal of "ischemic" kidney in rabbits with unilateral renal hypertension as compared to unilateral nephrectomy in normal rabbits. *Am J Physiol* *158* 438 1949

165 SCHROEDER, H A., AND GOLDMAN M L. Arterial hypertension in dogs. I Methods *Circulation* 5:730 1952

166 SMITH H W Hypertension and urologic disease *Am J Med* 4:?4 1948

167 SCHROEDER, H A. AND FISH G W Studies on "essential" hypertension. III. The effect of nephrectomy upon hypertension associated with organic renal disease *Am J M Sc* *199*:601 1940

168 PERRY H M., JR. AND SCHROEDER, H A Studies on the control of hypertension by Hyphex. III Pharmacological and chemical observations on 1 hydrazinophthalazine *Am J M Sc* ??8:396 1954

168b PERRY H M JR., AND SCHROEDER, H A The chemistry and pharmacology of 1 hydrazinophthalazine *Am J Med* *16*:606 1954

168c. PERRY H. M JR. AND SCHROEDER, H A Pharmacology of hydralazine. Proc. Second World Congress of Cardiology and Am Heart A 1954 p 442

169 SINCLAIR H M Pyridoxal phosphate as coenzyme of histaminase. *Biochem J* 51:x 1952.

170. BIEHL, J P AND VILTER, R. W Effect of isoniazid on vitamin B_6 metabolism its possible significance in producing isoniazid neuritis *Proc Soc Exper Biol & Med* *85* 339 1954

171 SCHULER, W Inhibition of diaminoxidase (histaminase) *Experientia* 8:230 1952.

172 GROSS F SCHULER, W TRIPOD J AND MEIER, R. Inhibition of

158 YUILE, C. L. Obstructive lesions of the main renal artery in relation to hypertension. *Am J M Sc* 07:394 1944

159 CASTLEMAN B and SMITHWICK R. H The relation of vascular disease to the hypertensive state *New England J Med* 239:732, 1948

160 WILSON C. AND BYROM F B Renal changes in malignant hypertension. *Lancet* 1 136 1939

161 SCHROEDER H A Arterial hypertension in rats I. Methods *J Exper Med* 75:513 1942

162 SCHROEDER H A., AND NEUMANN C., Arterial hypertension in rats. II. Effects on the kidneys. *J Exper Med* 75 527 1942

163 SPITZNAGEL, J K., AND SCHROEDER, H A Experimental pyelonephritis and hypertension in rats *Proc Soc Exper Biol & Med.*, 77:762 1951

164 FLASHER J AND DRURY D F Effects of removal of "ischemic" kidney in rabbits with unilateral renal hypertension as compared to unilateral nephrectomy in normal rabbits. *Am J Physiol* 158 438 1949

165 SCHROEDER, H A., AND GOLDMAN M L. Arterial hypertension in dogs. I Methods *Circulation* 5:730 1952

166 SMITH H W Hypertension and urologic disease *Am J Med* 4:724 1948

167 SCHROEDER, H A. AND FISH G W Studies on "essential" hypertension. III. The effect of nephrectomy upon hypertension associated with organic renal disease *Am J M Sc* 199:601 1940

168 PERRY H M., JR. AND SCHROEDER, H A Studies on the control of hypertension by Hyphex. III Pharmacological and chemical observations on 1 hydrazinophthalazine *Am J M Sc* 228:396 1954

168b PERRY H M JR., AND SCHROEDER, H A The chemistry and pharmacology of 1 hydrazinophthalazine *Am J Med* 16:606 1954

168c. PERRY H. M JR. AND SCHROEDER, H A Pharmacology of hydralazine. Proc. Second World Congress of Cardiology and Am Heart A 1954 p 442

169 SINCLAIR H M Pyridoxal phosphate as coenzyme of histaminase. *Biochem J* 51:x 1952.

170. BIEHL, J P AND VILTER, R. W Effect of isoniazid on vitamin B_6 metabolism its possible significance in producing isoniazid neuritis *Proc Soc Exper Biol & Med* 85 339 1954

171 SCHULER, W Inhibition of diaminoxidase (histaminase) *Experentia* 8:230 1952.

172 GROSS F SCHULER, W TRIPOD J AND MEIER, R. Inhibition of

Rheumatic and febrile syndrome during prolonged hydralazine treatment. *J.A.M.A.* 154:23 1954
185 PERRY H M JR. AND SCHROEDER, H A.. Syndrome simulating collagen disease caused by hydralazine (Apresoline) *J.A.M.A.*, 154 670 1954
186 COMENS P., AND SCHROEDER H A.. The L. E cell as a manifestation of delayed hydralazine intoxication *J.A.M.A.*, 160 1134 1956
187 SHACKMAN N H SWILLER A. I., AND MORRISON M.. Syndrome simulating acute disseminated lupus erythematosus Appearance after hydralazine (Apresoline) therapy *J.A.M.A.*, 155 1492 1954
188 COMENS P.. Experimental hydralazine disease and its similarity to disseminated lupus erythematosus *J Lab & Clin Med.*, 47 444 1956
189 SCHROEDER H A.. The effect of 1 hydrazinophthalazine in hypertension *Circulation* 5 28 1952
190 SZENT GYORGI A. *The Contraction Cycle and Its Regulation* Proc. Annual Meeting For High Blood Pressure Research Am Heart A., 1954
191 VILTER, R. W., MUELLER, J F GLAZER, H S., JARROLD T., ABRAHAM J THOMPSON C., AND HAWKINS, V R. The effect of vitamin B deficiency induced by desoxypyridoxine in human beings *J Lab & Clin Med.*, 42 335 1953
192 SINGH S I. AND SINGH L. The action of calcium on blood vessels and its relation to hypertension. *Proc Indian Acad Sc.*, 42 191 1955
192b SINGH S I. AND SINGH I. The action of sodium and potassium on blood vessels and its relation to hypertension. *Proc Indian Acad Sc* 42 172 1955
193 OLSEN N S., AND MARTINDALE, W E.. Hypertension and pyridoxine deficiency in the rat. *J Clin Investigation* 31 652 1952
193b OLSEN N S. AND MARTINDALE W E. Relation of pyridoxine deficiency and hypertension in the rat. *Federation Proc* 11 115 1952
194 OLSEN N S AND MARTINDALE, W E. Studies on chronic *vitamin* B_6 deficiency in the rat I. Changes in the intact animal *J Nutrition* 53 317 1954.
195 OLSEN N S AND MARTINDALE, W E *Studies* on chronic vitamin B deficiency in the rat. II. Changes in tissue metabolism *J Nutrition* 53 329 1954
196 HARRIS S. A.. Chemistry of vitamin B_6. IV Reactions in solutions at elevated temperatures *J Am Chem Soc* 63 3363 1941
197 GYÖRGY P Investigations on the vitamin B_2 complex. III The inactivation of lactoflavin and vitamin B by visible light. *Biochem J.*, 29 767 1935

Rheumatic and febrile syndrome during prolonged hydralazine treatment. *J.A.M.A.* *154*:23. 1954

185 PERRY H M JR. AND SCHROEDER, H A.. Syndrome simulating collagen disease caused by hydralazine (Apresoline) *J.A.M.A.*, *154* 670 1954

186 COMENS P., AND SCHROEDER H A.. The L. E. cell as a manifestation of delayed hydralazine intoxication *J.A.M.A.*, *160* 1134 1956

187 SHACKMAN N H SWILLER A. I., AND MORRISON M.. Syndrome simulating acute disseminated lupus erythematosus Appearance after hydralazine (Apresoline) therapy *J.A.M.A.*, *155* 1492 1954

188 COMENS P.. Experimental hydralazine disease and its similarity to disseminated lupus erythematosus *J Lab & Clin Med.*, *47* 444 1956

189 SCHROEDER H A.. The effect of 1 hydrazinophthalazine in hypertension *Circulation* *5* 28 1952

190 SZENT GYORGI A. *The Contraction Cycle and Its Regulation* Proc. Annual Meeting For High Blood Pressure Research Am Heart A., 1954

191 VILTER, R. W., MUELLER, J F GLAZER, H S., JARROLD T., ABRAHAM J THOMPSON C., AND HAWKINS, V R. The effect of vitamin B deficiency induced by desoxypyridoxine in human beings *J Lab & Clin Med.*, *42*:335 1953

192 SINGH S I. AND SINGH L. The action of calcium on blood vessels and its relation to hypertension. *Proc Indian Acad Sc.*, *42* 191 1955

192b SINGH S I. AND SINGH I. The action of sodium and potassium on blood vessels and its relation to hypertension. *Proc Indian Acad Sc* *42* 172 1955

193 OLSEN N S., AND MARTINDALE, W E.. Hypertension and pyridoxine deficiency in the rat. *J Clin Investigation* *31*:652 1952

193b OLSEN N S., AND MARTINDALE W E. Relation of pyridoxine deficiency and hypertension in the rat. *Federation Proc* *11* 115 1952

194 OLSEN N S AND MARTINDALE, W E. Studies on chronic vitamin B_6 deficiency in the rat I. Changes in the intact animal *J Nutrition* *53* 317 1954.

195 OLSEN N S AND MARTINDALE, W E *Studies* on chronic vitamin B deficiency in the rat. II. Changes in tissue metabolism *J Nutrition* *53* 329 1954

196 HARRIS S. A.. Chemistry of vitamin B_6. IV Reactions in solutions at elevated temperatures *J Am Chem Soc* *63* 3363 1941

197 GYÖRGY P Investigations on the vitamin B_2 complex. III The inactivation of lactoflavin and vitamin B by visible light. *Biochem J.*, *29*:767 1935

tous embolization with emphasis on an etiology of renal hyper tension *Am J Med* 20 366 1956

214 CORCORAN A. C TAYLOR, R. D., AND PAGE, I H.. Functional pat terns in renal disease *Ann Int Med* 28 560 1948

215 SNELL, E. E.. Summary of known metabolic functions of nicotinic acid riboflavin and vitamin B_6 *Physiol Rev* 33 509 1953

216 SELYE, H.. The role of the adrenal cortex in the pathogenesis of experimental hypertension in *Hypertension a Symposium* edited by Bell E. T Minneapolis Univ Minnesota Press 1951 pp 119 132.

217 BRAUN MENÉNDEZ E.. The mechanism of hypertension due to desoxycorticosterone in *Hypertension a Symposium* edited by Bell E. T Minneapolis Univ Minnesota Press 1951 pp 133 146

218 MASSON G M C. LEWIS L. A CORCORAN A C AND PAGE I H Desoxycorticosterone in rabbits Simulation of rabbit "toxemia of p[illegible]

218b RE[illegible]

[illegible]

re a[illegible] aspects of water metabolism Federation Proc., 1[illegible] 360 1953

218c. RENZI A A AND GAUNT R Apresoline (l hydrazinophthalazine) in the experimental eclampsia like syndrome and related aspects of water metabolism *Am J Physiol* 175 313 1953

218d. GAUNT R. ANTONCHAK N MILLER G J AND RENZI A A Effect of reserpine (serpasil) and hydralazine (apresoline) on experi mental steroid hypertension. *Am J Physiol* 187 63 1955

219 SAPIRSTEIN L. A BRANDT W L. AND DRURY D R. Production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water *Proc Soc Exper Biol & Med* 73 8? 19 0

220 GOLDMAN M L. KRISS J P SCHROEDER H A AND DAVIES D F The relation of the kidney to the acute pressor action of desoxy corticosterone *Am J M Sc* 222 257 1951

221 GOLDMAN M L AND SCHROEDER, H A The immediate pressor effect of desoxycorticosterone acetate *Science* 107 272 1948

221b GOLDMAN M L. AND SCHROEDER, H A Immediate pressor effect of desoxycorticosterone acetate in arterial hypertension. *Am J Med* 5 33 1948

222 GOLDMAN M L. RONZONI E AND SCHROEDER, H A The response of the adrenal cortex of the rat to dietary sa[illegible] replacem[illegible]

222b SCHROEDER [illegible]
MacBryc [illegible] 1951

tous embolization with emphasis on an etiology of renal hypertension *Am J Med* 20 366 1956
214 CORCORAN A. C TAYLOR, R. D., AND PAGE, I H.. Functional patterns in renal disease *Ann Int Med* 28 560 1948
215 SNELL, E. E.. Summary of known metabolic functions of nicotinic acid riboflavin and vitamin B, *Physiol Rev* 33 509 1953
216 SELYE, H.. The role of the adrenal cortex in the pathogenesis of experimental hypertension in *Hypertension a Symposium* edited by Bell E. T Minneapolis Univ Minnesota Press 1951 pp 119 132.
217 BRAUN MENÉNDEZ E.. The mechanism of hypertension due to desoxycorticosterone in *Hypertension a Symposium* edited by Bell E. T Minneapolis Univ Minnesota Press 1951 pp 133 146
218 MASSON G M C. LEWIS L. A CORCORAN A C AND PAGE I H Desoxycorticosterone in rabbits Simulation of rabbit "toxemia of n egnancy ...
218b Re...
...
... aspects of water metabolism Federation Proc., 1? 360 1953
218c. RENZI A A AND GAUNT R Apresoline (1 hydrazinophthalazine) in the experimental eclampsia like syndrome and related aspects of water metabolism *Am J Physiol* 175 313 1953
218d. GAUNT R. ANTONCHAK N MILLER G J AND RENZI A A Effect of reserpine (serpasil) and hydralazine (apresoline) on experimental steroid hypertension. *Am J Physiol* 187 63 1955
219 SAPIRSTEIN L. A BRANDT W L. AND DRURY D R. Production of hypertension in the rat by substituting hypertonic sodium chloride solutions for drinking water *Proc Soc Exper Biol & Med* 73 87 19 0
220 GOLDMAN M L. KRISS J F SCHROEDER H A AND DAVIES D F The relation of the kidney to the acute pressor action of desoxycorticosterone *Am J M Sc* 222 257 1951
221 GOLDMAN M L AND SCHROEDER, H A The immediate pressor effect of desoxycorticosterone acetate *Science* 107 272 1948
221b GOLDMAN M L. AND SCHROEDER, H A Immediate pressor effect of desoxycorticosterone acetate in arterial hypertension. *Am J Med* 5 33 1948
222. GOLDMAN M L RONZONI E AND SCHROEDER, H A The response of the adrenal cortex of the rat to dietary sal... replacem...
222b SCHROEDER ...
MacBryc ... 1951

234. BAILAR, J. *Chemistry of Coordinate Compounds* New York Reinhold, 1956
235 WILLIAMS R. P J Metal ions in biological systems *Biol Rev*., 28 331 1953
236 NAJJAR, V The role of metal ions in enzyme systems in *Phosphorus Metabolism* Vol. 1 McElroy W D and Glass B., editors Baltimore Johns Hopkins Press 1951 pp 500 520
237 METZLER, D E., IKAWA, M AND SNELL, E. E. A general mechanism for vitamin B_6-catalyzed reactions *J Am Chem Soc* 76 648 1954
238 VALLEE, B L Zinc and metallo-enzymes in *Advances in Protein Chemistry* Vol. X. New York Interscience 1955
239 HAMILTON J G AND SOLEY M H. Comparison of metabolism of iodine and of element 85 (eka iodine) *Proc Nat Acad Sc* 6 483 1940
240 BAUMAN E J., ZIZMER, N., OSHRY E., AND SEIDLIN S M Behavior of thyroid toward elements of seventh periodic group rhenium. *Proc Soc Exper Biol & Med* 72 502 1949
241 BAUMAN E. J SEARLE N Z., YALOW A A SIEGEL E. AND SEIDLIN S M Behavior of thyroid toward elements of seventh periodic group technetium *Federation Proc* 11 184 1952
242 RAY T W AND DEYSACH L J Storage of manganese by thyroid Effect on oxygen consumption of guinea pig *Proc Soc Exper Biol & Med*., 51 228 1942
243 GURD F R. N The specificity of metal protein interactions in *Ion Transport Across Membranes* edited by H T Clarke New York Acad Press 1954
244 RAY C T THREEFOOT S., AND BURCH G E. A study of the use of Rb^{86} as a tracer for measurement of Rb^{86} and K^{42} space and mass in intact man with and without congestive heart failure *J Clin Investigation* 33 9,7 1954
245 COLOWICK, S P AND KAPLAN N D *Methods in Enzymology* Vol 1 New York Acad Press 1955
246 LERNER, A B Metabolism of phenylalanine and tyrosine in *Advances in Enzymology* Vol 14 Nord F F editor New York Interscience 1953 pp 73 124
247 LERNER, A B., AND FITZPATRICK, T B., Biochemistry of melanin formation *Physiol Rev*., 30 91 1950
248 CURRAN G L. Effect of certain transition group elements on hepatic synthesis of cholesterol in the rat. *J Biol Chem* 210 765 1954
249 FOREMAN H VIER, M AND MAGEE M The metabolism of C^{14}-labelled ethylenediaminetetraacetic acid in the rat. *J Biol Chem* 203 1045 1953

34. Bailar, J., *Chemistry of Coordinate Compounds* New York Reinhold, 1956

235 Williams R. P J Metal ions in biological systems *Biol Rev.*, 28 381 1953

236 Najjar, V The role of metal ions in enzyme systems in *Phosphorus Metabolism* Vol. 1 McElroy W D and Glass B., editors Baltimore Johns Hopkins Press 1951 pp 500 520

237 Metzler, D E., Ikawa, M and Snell, E. E. A general mechanism for vitamin B_6-catalyzed reactions *J Am Chem Soc* 76 648 1954

238 Vallee, B L. Zinc and metallo-enzymes in *Advances in Protein Chemistry* Vol. X. New York Interscience 1955

239 Hamilton J G and Soley M H., Comparison of metabolism of iodine and of element 85 (eka iodine) *Proc Nat Acad Sc* 6 483 1940

240 Baumann E J., Zizmer, N., Oshry E., and Seidlin S M Behavior of thyroid toward elements of seventh periodic group rhenium. *Proc Soc Exper Biol & Med* 72 502 1949

241 Baumann E. J Searle N Z., Yalow A A Siegel E. and Seidlin S M Behavior of thyroid toward elements of seventh periodic group technetium *Federation Proc* 11 184 19 2

242 Ray T W and Deysach L J Storage of manganese by thyroid Effect on oxygen consumption of guinea pig *Proc Soc Exper Biol & Med.*, 51 228 1942

243 Gurd F R. N The specificity of metal protein interactions in *Ion Transport Across Membranes* edited by H T Clarke New York Acad Press 1954

244 Ray C T Threefoot S., and Burch G E. A study of the use of Rb^{86} as a tracer for measurement of Rb^{86} and K^{42} space and mass in intact man with and without congestive heart failure *J Clin Investigation* 33 9,7 1954

245 Colowick, S P and Kaplan N D Methods in *Enzymology* Vol 1 New York Acad Press 1955

246 Lerner, A B Metabolism of phenylalanine and tyrosine in *Advances in Enzymology* Vol 14 Nord F F editor New York Interscience 1953 pp 73 124

247 Lerner, A B., and Fitzpatrick, T B., Biochemistry of melanin formation *Physiol Rev.*, 30 91 1950

248 Curran G L. Effect of certain transition group elements on hepatic synthesis of cholesterol in the rat. *J Biol Chem* 210 765 1954

249 Foreman H Vier, M and Magee M The metabolism of C^{14}-labelled ethylenediaminetetraacetic acid in the rat. *J Biol Chem* 203 1045 1953

267 LEHNINGER, A L., Role of metal ions in enzyme systems *Physiol Rev*., 30 393 1950

268 BERTRAND D Distribution of vanadium among the invertebrates and vertebrates *Bull Soc chim biol* 25 36 1943

269 BERTRAND D Vanadium as an essential trace element for asper gillus niger *Ann Inst Pasteur* 68 226 1942.

270 BERTRAND D Vanadium in fungi especially amanita, *Bull Soc chim biol* 25 194 1943

271 BERTRAND D Distribution of vanadium in plants. Compt rend *Acad sc*., 212 11 0 1941

272 BERNHEIM F AND BERNHEIM M L. C. The effect of titanium on the oxidation of sulfhydryl groups by various tissues. J Biol Chem 127 69, 1939

273 PERRY H M., JR. SCHROEDER H A., AND PERRY B F., Abnormally high urinary cadmium and manganese in hypertensive patients *Proc Soc Exper Biol & Med* 1957 (In press)

274 BERNHEIM F., AND BERNHEIM M L. C. The action of vanadium on the oxidation of phospholipids by certain tissues J Biol *Chem* 127 353 1939

275 BERNHEIM F., AND BERNHEIM M L. C.. Note on the action of manganese and some other metals on the oxidation of certain substances by liver *J Biol Chem*., 128 79 1939

276 JACKSON D E The pharmacologic actions of vanadium *J Phar macol & Exper Therap* 3 477 1912

277 PERRY H M., JR. TEITELBAUM S AND SCHWARTZ P L. Effects of antihypertensive agents on amino acid decarboxylation and amine oxidation *Federation P oc* 14 113 1955

278. MYERS V C. AND MULL J W The influence of the administration of aluminum upon the aluminum content of the tissues and upon the growth and reproduction of rats *J Biol Chem* 78 605 1928

278b MYERS V C., AND MULL, J W The aluminum content of human autopsy tissue *J Biol Chem* 78 625 1928

279 MYERS V C., AND MORRISON D B., The influence of the administra tion of aluminum content of the tissues of the dog *J Biol Chem*., 78 615 1928

280 CURRAN G L., AND COSTELLO R L. Reduction of excess cholesterol in the rabbit aorta by inhibition of endogenous cholesterol syn thesis *J Exper Med* 103 49 1956

281 SINGH S I. AND SINGH I The action of lead on unstriated muscle and blood vessels and its relation to hypertension *Proc Indian Acad Sc* 42 62 1956

282. BARRETT H M., IRWIN D A., AND SEMMONS F., Studies on the

267 LEHNINGER, A L. Role of metal ions in enzyme systems *Physiol Rev.*, *30* 393 1950
268 BERTRAND D Distribution of vanadium among the invertebrates and vertebrates *Bull Soc chim biol* *25* 36 1943
269 BERTRAND D Vanadium as an essential trace element for asper gillus niger *Ann Inst Pasteur* 68 226 1942.
270 BERTRAND D Vanadium in fungi especially amanita. *Bull Soc chim biol* *25* 194 1943
271 BERTRAND D Distribution of vanadium in plants. Compt rend Acad sc., *212* 11 0 1941
272 BERNHEIM F AND BERNHEIM M L. C. The effect of titanium on the oxidation of sulfhydryl groups by various tissues. *J Biol Chem* *127* 69, 1939
273 PERRY H M., JR. SCHROEDER H A., AND PERRY B F., Abnormally high urinary cadmium and manganese in hypertensive patients *Proc Soc Exper Biol & Med* 1957 (In press)
274 BERNHEIM F., AND BERNHEIM M L. C. The action of vanadium on the oxidation of phospholipids by certain tissues *J Biol Chem* *127* 353 1939
275 BERNHEIM F., AND BERNHEIM M L C. Note on the action of manganese and some other metals on the oxidation of certain substances by liver *J Biol Chem.*, *128* 79 1939
276 JACKSON D E The pharmacologic actions of vanadium *J Pharmacol & Exper Therap* *3* 477 1912
277 PERRY H M., JR. TEITELBAUM S AND SCHWARTZ P L. Effects of antihypertensive agents on amino acid decarboxylation and amine oxidation Federation P oc 14 113 1955
278. MYERS V C. AND MULL J W The influence of the administration of aluminum upon the aluminum content of the tissues and upon the growth and reproduction of rats *J Biol Chem* *78* 605 1928
278b MYERS V C., AND MULL, J W The aluminum content of human autopsy tissue *J Biol Chem* 78 625 1928
279 MYERS V C., AND MORRISON D B., The influence of the administra tion of aluminum content of the tissues of the dog *J Biol Chem.*, *78* 615 1928
280 CURRAN G L., AND COSTELLO R L. Reduction of excess cholesterol in the rabbit aorta by inhibition of endogenous cholesterol syn thesis *J Exper Med* *103* 49 1956
281 SINGH S I. AND SINGH I The action of lead on unstriated muscle and blood vessels and its relation to hypertension *Proc Indian Acad Sc* 42 62 1956
282. BARRETT H M., IRWIN D A., AND SEMMONS F., Studies on the

297 DOMAR, G FREDGA A., AND LINDERHOLM H A method for quantitative determination of tetraethylthiuram disulphide (antabuse abstinyl) and its reduced form diethyldithiocarbamic acid as found in excreta *Acta chem scandinav* 3 1441 1949

298 DUBOIS K. P., COCHRAN K. W., AND MAZUR, M Inhibition of phosphatases by beryllium and antagonism of the inhibition by manganese. *Science* 110 420 1949

299 BOWEN W J., AND KERWIN T D A study of the effects of ethylene diaminetetraacetic acid on myosin adenosinetriphosphatase *J Biol Chem.* 211:237 1954

300 SMITH E. L., AND SPACKMAN D H Leucine amino-peptidase. V Activation, specificity and mechanism of action *J Biol Chem.*, 212:271 1955

301 HANSEN H T., AND SMITH E. L. Carnosinase An enzyme of swine kidney *J Biol Chem.*, 179:789 1949

302 WIELAND H AND MITCHELL, W Über den Mechanismus der Oxydationsvorgange XXIX. *Liebigs Ann Chem.*, 494 136 1932.

303 MAHLER, H. R., MACKLER, B., GREEN D E., AND BOCK R. M Studies on metalloflavoproteins III. Aldehyde oxidase A molybdoflavoprotein *J Biol Chem* 210 465 1954

304 WAELSCH H. Certain aspects of intermediary metabolism of glutamine asparagine and glutathione In *Advances in Enzymology* Vol. 13 Nord, F F., editor New York Interscience 1952 pp 237 315

305 SMITH E. L. The specificity of certain peptidases in *Advances in Enzymology* Vol. 12 Nord F F., editor New York, Interscience 1951 pp 191 257

306 SMITH E L. The glycylglycine dipeptidases of skeletal muscle and human uterus. *J Biol Chem* 173:571 1948

307 VALLEE B L. AND ALTSCHULE, M D. Zinc in the mammalian organism with particular reference to carbonic anhydrase *Physiol Rev* 29:370 1949

308 PERRY H M JR., SCHROEDER, H A., AND FREDERICKSON A. F. Urinary trace metals from normal and treated and untreated hypertensive patients *J Lab & Clin Med* 44:907 1954

309 PERRY H. M JR. AND SCHROEDER, H A Concentration of trace metals in urine of treated and untreated hypertensive patients compared with normal subjects *J Lab & Clin Med* 46:936 1955

310 PERRY H M JR., AND SCHROEDER, H A Comparison of the concentration of several trace metals in the urine of treated and untreated malignant hypertensive patients as compared with normal individuals *Circulation* 1 758 1955

297 DOMAR, G FREDGA A., AND LINDERHOLM H A method for quanti tative determination of tetraethylthiuram disulphide (antabuse abstinyl) and its reduced form diethyldithiocarbamic acid as found in excreta *Acta chem scandinav* 3 1441 1949

298 DUBOIS K. P., COCHRAN K. W., AND MAZUR, M Inhibition of phosphatases by beryllium and antagonism of the inhibition by manganese. Science *110* 420 1949

299 BOWEN W J., AND KERWIN T D A study of the effects of ethylene diaminetetraacetic acid on myosin adenosinetriphosphatase *J Biol Chem. 211*:237 1954

300 SMITH E. L., AND SPACKMAN D H Leucine amino-peptidase. V Activation, specificity and mechanism of action J Biol Chem., *212*:271 195

301 HANSEN H T., AND SMITH E. L. Carnosinase An enzyme of swine kidney J *Biol Chem., 179*:789 1949

302. WIELAND H AND MITCHELL, W Uber den Mechanismus der Oxydationsvorgange XXIX. *Liebigs Ann Chem., 491* 156 1932.

303 MAHLER, H. R., MACKLER, B., GREEN D E., AND BOCK R. M Studies on metalloflavoproteins III. Aldehyde oxidase A molybdo-flavoprotein J Biol Chem 210 465 1954

304. WAELSCH H., Certain aspects of intermediary metabolism of glu tamine asparagine and glutathione In *Advances in Enzymology* Vol. 13 Nord, F F., editor New York Interscience 1952 pp 237 315

305 SMITH E. L. The specificity of certain peptidases In *Advances in Enzymology* Vol. 12 Nord F F., editor New York, Interscience 1951 pp 191 257

306 SMITH E L. The glycylglycine dipeptidases of skeletal muscle and human uterus. *J Biol Chem 173*:571 1948

307 VALLEE B L. AND ALTSCHULE, M D., Zinc in the mammalian or ganism with particular reference to carbonic anhydrase *Physiol Rev 29*:370 1949

308 PERRY H M JR., SCHROEDER, H A., AND FREDERICKSON A. F., Urinary trace metals from normal and treated and untreated hypertensive patients *J Lab & Clin Med 44*:907 1954

309 PERRY H. M JR. AND SCHROEDER, H A Concentration of trace metals in urine of treated and untreated hypertensive patients compared with normal subjects *J Lab & Clin Med 46*:936 195

310 PERRY H M JR., AND SCHROEDER, H A Comparison of the con centration of several trace metals in the urine of treated and un treated malignant hypertensive patients as compared with normal individuals *Circulation 1* 758 1955

lationship to human arteriosclerosis Arch Path 20 81 125 253-304 1935

524 Greenberg L. D., and Rinehart J F Plasma cholesterol levels of cholesterol fed control and pyridoxine deficient monkeys *Proc Soc Exper Biol & Med.*, 76 580 1951

524b. Rinehart J F., and Greenberg L. D., Arteriosclerotic lesions in pyridoxine-deficient monkeys *Am J Path.*, 25 481 1949

525 Rinehart J F and Greenberg L. D Pathogenesis of experimental arteriosclerosis in pyridoxine deficiency With notes on similarities to human arteriosclerosis *Arch Path.*, 51 12 1951

526 Mushett C. W., and Emerson G A Arteriosclerosis in pyridoxine-deficient monkeys and dogs *Federation Proc* 15 526 1956.

527 Aschoff L. *Lectures on Pathology* New York Hoeber 1924 p 131

528 Movat H Z and More, R. H Morphologic and histochemical studies on the development and progression of arteriosclerosis *Circulation* 12 481 19 5

529 Strong J P McGill, H C. Jr., Griffin O R., and Holman R. L. Natural history of aortic atherosclerosis, ages 1 to 40 *Federation Proc.*, 15 535 1956

530 Andrus S B Mann G V Fillios L. C., and Stare, F J Early histologic changes in experimental atherosclerosis. *Federation Proc* 15 542 1956

531 Curran G L., and Clute, O L. Effect of cations on cholesterol synthesis by surviving rat liver *J Biol Chem* 04 215 1953

532 Rodahl, K Studies on the Blood and Blood Pressure in the Eskimo and the Significance of Ketosis under *Arctic Conditions Norsk Polarinstitutt Skrifter* Nr 102 Oslo 1954

533 Larsen N P Stress and the aging circulation *Am Pract & Digest Treatment* 6 1681 1955

534 Kuczynski B., Pathologische-geographische Untersuchungen in der Kirgesischdsungarischen Steppe. *Klin Wchnschr* 4 39 1925

535 Clawson B J *The heart in essential hypertension* in *Hypertension A Symposium edited by Bell E. T* Minneapolis Univ Minnesota Press 1951 pp 539 553

536. Goldstein F Jenson W K. Waldron J M and Duncan G G The relationship between hypertension and coronary occlusion *Ann Int Med* 44 446 19 6

536 Holman R. L. Necrotizing arteritis in dogs produced by a combination of high fat diet experimental renal insufficiency in *Factors Regulating Blood Pressure* Transactions of the Fourth Conference ed. by Zweifach B W., and Shorr E New York, Macy 1950 p 150

537 Fillios L. C., Andrus S B., Mann G V., and Stare F J Experimental atherosclerosis in the rat. *Federation Proc* 15 550 1956

lationship to human arteriosclerosis *Arch Path* 20 81 125 253-304 1935

324 Greenberg L. D., and Rinehart J F Plasma cholesterol levels of cholesterol fed control and pyridoxine deficient monkeys *Proc Soc Exper Biol & Med.*, 76 380 1951

324b. Rinehart J F., and Greenberg L. D., Arteriosclerotic lesions in pyridoxine-deficient monkeys *Am J Path.*, 25 481 1949

325 Rinehart J F and Greenberg L. D Pathogenesis of experimental arteriosclerosis in pyridoxine deficiency With notes on similarities to human arteriosclerosis *Arch Path.*, 51 12 1951

326 Mushett C. W., and Emerson G A Arteriosclerosis in pyridoxine-deficient monkeys and dogs *Federation Proc* 15 526 1956.

327 Aschoff L. *Lectures on Pathology* New York Hoeber 1924 p 131

328 Movat H Z and More, R. H Morphologic and histochemical studies on the development and progression of arteriosclerosis *Circulation* 12 481 1955

329 Strong J P McGill, H C Jr., Griffin O R., and Holman R. L. Natural history of aortic atherosclerosis, ages 1 to 40 *Federation Proc.*, 15 535 1956

330 Andrus S B Mann G V Fillios L. C., and Stare, F J Early histologic changes in experimental atherosclerosis. *Federation Proc* 15 542 1956

331 Curran G L., and Clute, O L. Effect of cations on cholesterol synthesis by surviving rat liver *J Biol Chem* 04 215 1953

332 Rodahl, K Studies on the Blood and Blood Pressure in the Eskimo and the Significance of Ketosis under Arctic Conditions *Norsk Polarinstitutt Skrifter* Nr 102 Oslo 1954

333 Larsen N P Stress and the aging circulation *Am Pract & Digest Treatment* 6 1681 1955

334 Kuczynski B., Pathologische-geographische Untersuchungen in der Kirgesischdsungarischen Steppe. *Klin Wchnschr* 4 59 1925

335 Clawson B J The heart in essential hypertension in *Hypertension A Symposium edited by Bell E. T* Minneapolis Univ Minnesota Press 1951 pp 439-453

335b. Goldstein F Jenson W K. Waleson J M and Duncan G G The relationship between hypertension and coronary occlusion *Ann Int Med* 44 446 1956

336 Holman R. L., Necrotizing arteritis in dogs produced by a combination of high fat diet experimental renal insufficiency in *Factors Regulating Blood Pressure* Transactions of the Fourth Conference ed. by Zweifach B W., and Shorr E New York, Macy 1950 p 150

337 Fillios L. C., Andrus S B., Mann G V., and Stare F J Experimental atherosclerosis in the rat. *Federation Proc* 15 550 1956

ships in human plasma atherosclerosis and related conditions. *Am J Med 11* 480 1951

355 BARR, D P Influence of sex and sex hormones upon the develop ment of atherosclerosis and upon the lipoproteins of plasma *J Chronic Dis 1* 63 1955

356 KATZ L. N., AND STAMLER, J *Experimental Atherosclerosis* Spring field, Thomas 1953

357 KEYS A The physiology of the individual as an approach to a more quantitative biology of man. *Federation Proc., 8* 523 1949

358. KEYS A ANDERSON J T., MICKELSEN O Serum cholesterol in men in basal and nonbasal states *Science 123* 29 1956

358b LIN T M., KARVINEN E., AND IVY A. C. Absorption of dietary cholesterol in man *Federation Proc 15* 120 1956

359 TURNER, K. B AND STEINER, A A long term study of the variation of serum cholesterol in man. *J Clin Investigation 18* 45 1939

360 DEUEL, H. J JR., The Lipids Vol 2 New York Interscience 1955

361 AFTERGOOD L., ALFIN SLATER, R. B., AND DEUEL, H J., JR. Compara tive effect of cottonseed oil and lard on cholesterol metabolism in the rat. *Federation Proc 15* 541 1956

362. LANGDON R. G III Some aspects of cholesterol metabolism related to atherosclerosis in *Fat Metabolism* edited by Najjar V A Baltimore Johns Hopkins Press 1954 pp 162 181

363 KINSELL, L. W MICHAELS G D COCHRANE G C., PARTRIDGE J W., JAHN J J AND BALCH H E. Effect of vegetable fat on hyper cholesterolemia and hyperphospholipidemia. *J Am Diabetes A., 3* 113 1954

364 KINSELL, L. W Personal communication

365 FRISKEY R. W., MICHAELS G D AND KINSELL, L. W Observations regarding the effects of unsaturated fats *Circulation 12* 492 1955

366 JONES R. J AND REISS O K. The hypocholesteremic effect of a hot alcoholic extract of brain in hypercholesteremic patients. *Circulation 12* 496 1955

367 AHRENS E H., JR. TSALTAS T T., HIRSCH J., AND INSULL, W., JR. Effects of dietary fats on the serum lipides of human subjects *J Clin Investigation 34* 918 1955

368. BEVERIDGE, J M R., CONNELL, W F AND MAYER, G Further studies on dietary factors affecting plasma lipid levels in humans. *Circulation 12* 499 1955

369 PETERSON D W., NICHOLS C. W., JR., PEEK, N F AND CHAIKOFF I L. Depression of plasma cholesterol in human subjects con suming butter containing soy sterols. *Federation Proc 15* 569 1956

370 TULPULE, P G., AND PATWARDHAN V N The effect of fat and

ships in human plasma atherosclerosis and related conditions. *Am J Med 11* 480 1951
355 BARR, D P Influence of sex and sex hormones upon the development of atherosclerosis and upon the lipoproteins of plasma *J Chronic Dis 1* 63 1955
356 KATZ L. N., AND STAMLER, J *Experimental Atherosclerosis* Springfield, Thomas 1953
357 KEYS A The physiology of the individual as an approach to a more quantitative biology of man. *Federation Proc., 8* 523 1949
358. KEYS A ANDERSON J T., MICKELSEN O Serum cholesterol in men in basal and nonbasal states *Science 123* 29 1956
358b LIN T M., KARVINEN E., AND IVY A. C. Absorption of dietary cholesterol in man *Federation Proc 15* 120 1956
359 TURNER, K. B AND STEINER, A A long term study of the variation of serum cholesterol in man. *J Clin Investigation 18* 45 1939
360 DEUEL, H. J JR., The Lipids Vol 2 New York Interscience 1955
361 AFTERGOOD L., ALFIN SLATER, R. B., AND DEUEL, H J., JR. Comparative effect of cottonseed oil and lard on cholesterol metabolism in the rat. *Federation Proc 15* 541 1956
362. LANGDON R. G III Some aspects of cholesterol metabolism related to atherosclerosis in *Fat Metabolism* edited by Najjar V A Baltimore Johns Hopkins Press 1954 pp 162 181
363 KINSELL, L. W MICHAELS G D COCHRANE G C., PARTRIDGE J W., JAHN J J AND BALCH H E. Effect of vegetable fat on hypercholesterolemia and hyperphospholipidemia. *J Am Diabetes A., 3* 113 1954
364 KINSELL, L. W Personal communication
365 FRISKEY R. W., MICHAELS G D AND KINSELL, L. W Observations regarding the effects of unsaturated fats *Circulation 12* 492 1955
366 JONES R. J AND REISS O K. The hypocholesteremic effect of a hot alcoholic extract of brain in hypercholesteremic patients. *Circulation 12* 496 1955
367 AHRENS E H., JR. TSALTAS T T., HIRSCH J., AND INSULL, W., JR. Effects of dietary fats on the serum lipides of human subjects *J Clin Investigation 34* 918 1955
368. BEVERIDGE, J M R., CONNELL, W F AND MAYER, G Further studies on dietary factors affecting plasma lipid levels in humans. *Circulation 12* 499 1955
369 PETERSON D W., NICHOLS C. W., JR., PEEK, N F AND CHAIKOFF I L. Depression of plasma cholesterol in human subjects consuming butter containing soy sterols. *Federation Proc 15* 569 1956
370 TULPULE, P G., AND PATWARDHAN V N The effect of fat and

cholesterol changes in nephrectomized dogs maintained by peritoneal dialysis Federation Proc., 15 118 1956

386 Anderson J T., Taylor H L. and Keys A Serum cholesterol in subjects on reducing diets high and low in fat Federation Proc., 15 549 1956

387 Krinsky N L, Cornwell, D G., and Oncley J L. Vitamin A carotenoids and plasma lipoproteins Federation Proc 15 115 1956

388 Schroeder, H A. Rapid spontaneous variations in blood pressure Federation Proc 8 1 1949

389 Wagener, H. P., and Keith N M Diffuse arteriolar disease with hypertension and the associated retinal lesions. Medicine 18 317 1939

390 Hellner O M Estimation of catechol amines in urine by means of a rabbit aortic strip as an aid to the diagnosis of pheochromocytoma J Lab & Clin Med 46 871 1955

391 Schroeder H A Studies on essential hypertension IV Early arterial hypertension Am J M Sc 204 62 1942.

392 Perera, G A Hypertensive vascular disease Therapeutic principles and objectives J Chronic Dis 1 472 1955

393 Schroeder H A. Steele, J M Studies in essential hypertension, II The association of hypertension with organic renal disease Arch Int Med 68 261 1941

394 Schroeder, H A and Steele, J M Abnormalities of the urinary tract in "essential hypertension Proc Soc Exper Biol & Med 39 107 1938

395 Grollman, A L. Surtshin S and Hedrick, J T Effects on essential hypertension of veriloid A new derivative of veratrum viride Arch Int Med 87 789 1951

396 Schroeder H A., Hydrallazine (Apresoline) in the control of severe hypertension Practitioner 173 195 1954

397 Schroeder H. A Renal failure associated with low extracellular sodium chloride The low salt syndrome J.A.M.A., 141 117 1949

398 Schroeder H A Goldman M L. Futcher, P H., and Hunter, M Low sodium chloride diets in hypertension. J.A.M.A., 140 458 1949

399 Schroeder H A Futcher P H., and Goldman M L The effects of the rice diet upon the blood pressure of hypertensive individuals Ann Int Med 30 713 1949

400 Schroeder H A and Perry H M Jr. Errors in the evaluation of hypertension Am. Heart J., 51 716 1956

401 Schroeder, H A The effect of 1 hydrazinophthalazine and hexamethonium on hypertension J Lab & Clin Med 38 949 1951

402 Schroeder, H A. Control of hypertension by hexamethonium and

cholesterol changes in nephrectomized dogs maintained by peritoneal dialysis *Federation Proc.*, 15 118 1956

386 ANDERSON J T., TAYLOR H L. AND KEYS A Serum cholesterol in subjects on reducing diets high and low in fat *Federation Proc.*, 15 54? 19 6

387 KRINSKY N L, CORNWELL, D G., AND ONCLEY J L. Vitamin A carotenoids and plasma lipoproteins *Federation Proc* 15 115 1956

388 SCHROEDER, H A. Rapid spontaneous variations in blood pressure *Federation Proc* 8 1 1949

389 WAGENER, H. P., AND KEITH N M Diffuse arteriolar disease with hypertension and the associated retinal lesions. *Medicine* 18 317 1939

390 HELMER O M Estimation of catechol amines in urine by means of a rabbit aortic strip as an aid to the diagnosis of pheochromocytoma *J Lab & Clin Med* 46 871 1955

391 SCHROEDER H A Studies on essential hypertension IV Early arterial hypertension *Am J M Sc* 204 62 1942.

392 PERERA, G A Hypertensive vascular disease: Therapeutic principles and objectives *J Chronic Dis* 1 472 1955

393 SCHROEDER H A. STEELE, J M Studies in "essential" hypertension. II The association of hypertension with organic renal disease *Arch Int Med* 68 261 1941

394 SCHROEDER, H A AND STEELE, J M Abnormalities of the urinary tract in "essential" hypertension *Proc Soc Exper Biol & Med* 39 107 1938

395 GROPPER, A L. SURTSHIN S AND HEDRICK, J T Effects on essential hypertension of veriloid A new derivative of *veratrum viride* *Arch Int Med* 87 789 1951

396 SCHROEDER H A. Hydrallazine (Apresoline) in the control of severe hypertension *Practitioner* 173 195 1954

397 SCHROEDER H. A Renal failure associated with low extracellular sodium chloride The low salt syndrome *J.A.M.A.*, 141 117 1949

398 SCHROEDER H A GOLDMAN M L. FUTCHER, P H., AND HUNTER, M Low sodium chloride diets in hypertension. *J.A.M.A.*, 140 458 1949

399 SCHROEDER H A FUTCHER P H., AND GOLDMAN M L The effects of the rice diet upon the blood pressure of hypertensive individuals *Ann Int Med* 30 713 1949

400 SCHROEDER H A AND PERRY H M JR. Errors in the evaluation of hypertension *Am. Heart J.*, 51 7?6 1956

401 SCHROEDER, H A The effect of 1 hydrazinophthalazine and hexamethonium on hypertension *J Lab & Clin Med* 38 949 1951

402 SCHROEDER, H A. Control of hypertension by hexamethonium and

cholesterol changes in nephrectomized dogs maintained by peritoneal dialysis *Federation Proc.*, *15* 118 1956
386 ANDERSON J T., TAYLOR H L. AND KEYS A Serum cholesterol in subjects on reducing diets high and low in fat. *Federation Proc* *15*.512 1956
387 KRINSKY N I., CORNWELL, D G., AND ONCLEY J L. Vitamin A carotenoids and plasma lipoproteins *Federation Proc* *15* 113 1956
388 SCHROEDER, H A. Rapid spontaneous variations in blood pressure *Federation Proc* *8* 1 1949
389 WAGENER, H P AND KEITH N M. Diffuse arteriolar disease with hypertension and the associated retinal lesions *Medicine* *18*:317 1939
390 HELMER, O M Estimation of catechol amines in urine by means of a rabbit aortic strip as an aid to the diagnosis of pheochromocytoma J *Lab & Clin Med* *46*:871 1955
391 SCHROEDER, H A Studies on essential hypertension IV Early arterial hypertension *Am J M Sc.*, *204*:67 1942.
392 PERERA G A Hypertensive vascular disease: Therapeutic principles and objectives *J Chronic Dis.*, *1* 472 1955
393 SCHROEDER H A STEELE, J M Studies in essential" hypertension II. The association of hypertension with organic renal disease *Arch Int Med* *68*:261 1941
394 SCHROEDER, H A., AND STEELE, J M Abnormalities of the urinary tract in essential hypertension *Proc Soc Exper Biol & Med.*, *39* 107 1938
395 GROPPER, A L SURTSHIN S AND HEDRICK J T Effects on essential hypertension of veriloid A new derivative of *veratrum viride* *Arch Int Med* *87*:789 1951
396 SCHROEDER, H A Hydrallazine (Apresoline) in the control of severe hypertension *Practitioner* *173* 195 1954
397 SCHROEDER H A Renal failure associated with low extracellular sodium chloride The low salt syndrome *J.A.M.A.*, *141* 117 1949
398 SCHROEDER H A., GOLDMAN M L. FUTCHER, P H AND HUNTER M Low sodium chloride diets in hypertension *J.A.M.A* *140* 458 1949
399 SCHROEDER, H A FUTCHER, P H AND GOLDMAN M L The effects of the rice diet upon the blood pressure of hypertensive individuals *Ann Int Med* *30*:713 1949
400 SCHROEDER H A AND PERRY H M., JR. Errors in the evaluation of hypertension *Am Heart J* *51*:776 1956
401 SCHROEDER, H A The effect of 1 hydrazinophthalazine and hexamethonium on hypertension *J Lab & Clin Med* *38*:949 1951
402 SCHROEDER, H A. Control of hypertension by hexamethonium and

cholesterol changes in nephrectomized dogs maintained by peri toneal dialysis *Federation Proc.*, 15 118 1956

386 ANDERSON J T., TAYLOR H L. AND KEYS A Serum cholesterol in subjects on reducing diets high and low in fat. *Federation Proc* 15 542 1956

387 KRINSKY N L., CORNWELL, D G., AND ONCLEY J L. Vitamin A carotenoids and plasma lipoproteins *Federation Proc* 15 113 1956

388 SCHROEDER, H A. Rapid spontaneous variations in blood pressure *Federation Proc* 8 1 1949

389 WAGENER, H P AND KEITH N M. Diffuse arteriolar disease with hypertension and the associated retinal lesions *Medicine* 18 317 1939

390 HELMER, O M Estimation of catechol amines in urine by means of a rabbit aortic strip as an aid to the diagnosis of pheochromocytoma *J Lab & Clin Med* 46 871 1955

391 SCHROEDER, H A Studies on essential hypertension IV Early arterial hypertension *Am J M Sc.*, 204 69 1942.

392 PERERA G A Hypertensive vascular disease Therapeutic principles and objectives *J Chronic Dis.*, 1 472 1955

393 SCHROEDER H A STEELE, J M Studies in essential" hypertension II. The association of hypertension with organic renal disease *Arch Int Med* 68 261 1941

394 SCHROEDER, H A., AND STEELE, J M Abnormalities of the urinary tract in essential hypertension *Proc Soc Exper Biol & Med.*, 39 107 1938

395 GROPPER, A L SCRTSHIN S AND HEDRICK J T Effects on essential hypertension of veriloid A new derivative of *veratrum viride* *Arch Int Med* 87 789 1951

396 SCHROEDER, H A Hydrallazine (Apresoline) in the control of severe hypertension *Practitioner* 173 195 1954

397 SCHROEDER H A Renal failure associated with low extracellular sodium chloride The low salt syndrome *J.A.M.A.*, 141 117 1949

398 SCHROEDER H A., GOLDMAN M L. FUTCHER, P H AND HUNTER M Low sodium chloride diets in hypertension *J.A.M.A* 140 458 1949

399 SCHROEDER, H A FUTCHER, P H AND GOLDMAN M L The effects of the rice diet upon the blood pressure of hypertensive individuals *Ann Int Med* 30 713 1949

400 SCHROEDER H A AND PERRY H M., JR. Errors in the evaluation of hypertension *Am Heart J* 51 776 1956

401 SCHROEDER, H A The effect of 1 hydrazinophthalazine and hexamethonium on hypertension *J Lab & Clin Med* 38 949 1951

402 SCHROEDER, H A. Control of hypertension by hexamethonium and

the hypertensive process when blood pressure is controlled by drugs. *Circulation* 12:759 1955
418. SCHROEDER, H A. AND PERRY H M., JR. Clinical Conference: The treatment of hypertension with modern drugs *Circulation* 13:98 1956
419 SCHROEDER, H A. Management of arterial hypertension *Am J Med.*, 17:540 1954
420 SMITHWICK, R. H BUSH R. D., KINSEY D., AND WHITELAW G P.. Hypertension and associated cardiovascular disease *J.A.M.A.*, 160 1023 1956
421 WHITE, P D.. Severe hypertension—study of one hundred patients with cardiovascular complications *J.A.M.A* 160 1027 1956
422. CLARKE, N E., CLARKE, C. N., AND MOSHER, R. E.. The "in vivo" dissolution of metastatic calcium An approach to atherosclerosis *Am J M Sc* 229 142 1955
423 LEE, R. E. SELIGMANN A M GOEBEL, D., FULTON L. A AND CLARK, M A., Reserpine-hydralazine combination therapy of hypertensive disease with hydralazine in doses generally below the "toxic range." *Ann Int Med.*, 44 456 1956
424. MEIER, R.. Antistine and related imidazolines. *Ann New York Acad Sc* 50 1161 1950
425 WILKINSON E L., BACKMAN H., AND HECHT H H Cardiovascular and renal adjustments to a hypotensive agent (1 hydrazinophthalazine) *J Clin Investigation* 31:872 1952.
426 REUBI F C. Renal hyperemia induced in man by a new phthalazine derivative *Proc Soc Exper Biol. & Med* 73 102 1950
427 MARKS P A., REYNELL, P C., AND BRADLEY S E., Hemodynamic effects of 1 hydrazinophthalazine in the dog, with special reference to circulating splanchnic blood volume *Am J Physiol.*, 183 144 1955
428 PICK R., STAMLER J RODBARD S AND KATZ L. N Inhibition of coronary atheromatosis in cholesterol fed chicks receiving estrogens. *Circulation* 4 468 1951
429 PICK, R., STAMLER, J., RODBARD S., AND KATZ L. N., Estrogen induced regression of coronary atherosclerosis in cholesterol fed chicks *Circulation* 6:858 1952
430 RIVIN A. U AND DIMITROFF S P The incidence and severity of atherosclerosis in estrogen treated males and in females with a hypoestrogenic or a hyperestrogenic state. *Circulation* 9 533 1954
431 WILENS S L. The resorption of arterial atheromatous deposits in wasting disease. *Am J Path.*, 23:793 1947
432. MEISTER, A., Metabolism of glutamine. *Physiol Rev.*, 36 103 1956

the hypertensive process when blood pressure is controlled by drugs. *Circulation* 12 759 1955

418. SCHROEDER, H A. AND PERRY H M., JR. Clinical Conference: The treatment of hypertension with modern drugs *Circulation* 13 98 1956

419 SCHROEDER, H A. Management of arterial hypertension *Am J Med.*, 17 540 1954

420 SMITHWICK, R. H BUSH R. D., KINSEY D., AND WHITELAW G P.. Hypertension and associated cardiovascular disease *J.A.M.A.*, 160 1023 1956

421 WHITE, P D.. Severe hypertension—study of one hundred patients with cardiovascular complications *J.A.M.A* 160 1027 1956

422. CLARKE, N E., CLARKE, C. N., AND MOSHER, R. E.. The "in vivo" dissolution of metastatic calcium An approach to atherosclerosis *Am J M Sc* 229 142 1955

423 LEE, R. E. SELIGMANN A M GOEBEL, D., FULTON L. A AND CLARK, M A., Reserpine-hydralazine combination therapy of hypertensive disease with hydralazine in doses generally below the "toxic range." *Ann Int Med.*, 44 456 1956

424. MEIER, R.. Antistine and related imidazolines. *Ann New York Acad Sc* 50 1161 1950

425 WILKINSON E L., BACKMAN H., AND HECHT H H Cardiovascular and renal adjustments to a hypotensive agent (1 hydrazinophthalazine) *J Clin Investigation* 31 872 1952.

426 REUBI F C. Renal hyperemia induced in man by a new phthalazine derivative *Proc Soc Exper Biol. & Med* 73 102 1950

427 MARKS P A., REYNELL, P C., AND BRADLEY S E.. Hemodynamic effects of 1 hydrazinophthalazine in the dog, with special reference to circulating splanchnic blood volume *Am J Physiol.*, 183 144 1955

428 PICK R., STAMLER J RODBARD S AND KATZ L. N Inhibition of coronary atheromatosis in cholesterol fed chicks receiving estrogens. *Circulation* 4 468 1951

429 PICK, R., STAMLER, J., RODBARD S., AND KATZ L. N.. Estrogen induced regression of coronary atherosclerosis in cholesterol fed chicks *Circulation* 6 858 1952

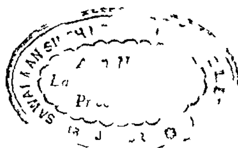
430 RIVIN A. U AND DIMITROFF S P The incidence and severity of atherosclerosis in estrogen treated males and in females with a hypoestrogenic or a hyperestrogenic state. *Circulation* 9 533 1954

431 WILENS S L. The resorption of arterial atheromatous deposits in wasting disease. *Am J Path.*, 23 793 1947

432. MEISTER, A.. Metabolism of glutamine. *Physiol Rev.*, 36 103 1956

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